

Review

Production and Synthetic Possibilities of 5-Chloromethylfurfural as Alternative Biobased Furan

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Abstract: As fossil-based resource depletion intensifies and the use of lignocellulosic biomass gains more and more momentum for the development of biorefineries, the production of furans has received a great deal of attention considering their outstanding synthetic possibilities. The production of 5-hydroxymethylfurfural (HMF) is quite established in the recent scientific literature, with a large number of studies having been published in the last few years. Lately, there has been a growing interest in the synthesis of 5-chloromethylfurfural (CMF) as a novel building block of similar molecular structure to that of HMF. CMF has some advantages, such as its production taking place at milder reaction conditions, a lower polarity that enables easier separation with the aid of organic media, and the presence of chlorine as a better leaving group in synthesis. Precisely the latter aspect has given rise to several interesting products to be obtained therefrom, including 2,5-dimethylfuran, 2,5-furandicarboxylic acid, and 5-methylfurfural, to name a few. This work covers the most relevant aspects related to the production of CMF and an array of synthetic possibilities. Through varied catalysts and reaction conditions, value-added products can be obtained from this chemical, thus highlighting the advances in the production and use of this chemical in recent years.

Keywords: 5-chloromethylfurfural; biomass; biofuels; biphasic systems; furans; reaction with in situ extraction

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1. Introduction

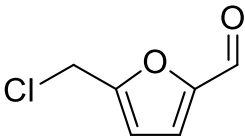
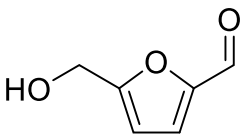
The increasing demand for dwindling fossil fuel-based resources drives innovation in the development of biobased and sustainable alternatives. In an effort to abide by different regulations setting targets for net zero emissions by 2050 and promoting the use of renewable resources for the development of bioeconomies, biorefineries are emerging as an industrial model [1–3]. Thus, a clear focus on an integrated approach to chemical production from biomass has been put forward in the last few years.

Lignocellulosic biomass is vastly abundant, comprising three major fractions, cellulose, hemicellulose, and lignin [4]. Furans are a promising class of platform chemicals identified by the United States Department of Energy (DoE) in 2004, and subsequently updated in 2010 [5,6]. Furans can be separated into those derived from hexose sugars, e.g., 5-hydroxymethylfurfural (HMF), and those from pentose sugars such as furfural [7,8] and products derived thereof. HMF and furfural owe their proven excellence as platform chemicals to the vast array of synthetic upgrade pathways available through the utilisation of the furan ring and aldehyde groups, with the additional hydroxyl group for HMF

[9,10]. Products that can be obtained by different reactions from both furans include bio-fuels, green solvents, and other molecules that can be used as monomers for the production of bioplastics, as is the case of 2,5-furandicarboxylic acid (FDCA) to yield polyethylene furanoate (PEF), a chemical analogue of polyethylene terephthalate (PET) [9,11].

Extensive reviews on the production, applications, and synthetic upgrade possibilities of HMF and furfural have already gained significant traction over recent years [7,8,12]. These reviews detail the production of furans using single-phase systems and introduce the concept of biphasic reaction with in situ extraction systems as a mitigation strategy to prevent reaction to undesired by-products. In this way, selectivity to the desired product is not only driven by catalyst design but also by the use of a multiphase operation. HMF readily rehydrates under aqueous conditions to levulinic acid (LA) and formic acid (FA), with additional self-condensation towards insoluble humin polymers under acidic media, which is also present with furfural. In situ product removal through the use of biphasic systems is becoming increasingly more widespread as a mitigation strategy to separate compounds that may be detrimental to system performance. Liquid–liquid extraction can enhance thermodynamically limited reactions and reduce compounds that may affect (bio)catalytic operation, as well as keeping molecular catalysts separated from products [13,14]. However, HMF as a platform chemical has certain drawbacks such as the ready rehydration towards the mentioned undesired side products due to the hydrophilicity caused by the hydroxyl moiety which results in limited partitioning in biphasic systems. Hence, efforts have been made to identify analogues of HMF that exhibit greater partitioning, such as 5-chloromethylfurfural (CMF) and, to a lesser extent, 5-bromomethylfurfural as an alternative halogenated furan [15,16]. CMF is of specific interest due to its very similar molecular structure to HMF, but the presence of the chlorine group confers CMF with good synthetic possibilities owing to it being a better-leaving group than the hydroxyl moiety of HMF. Additionally, this moiety makes its polarity lower, thus allowing potentially better separation by liquid–liquid extraction. Despite the first reports of its production dating as far back as 1901, the scarce characterisation (Table 1) of CMF in the open literature makes it obvious that there is still a lot to explore about this novel chemical [17]. Comparisons between HMF and CMF properties are limited due to the sparse data available for CMF; however, it can be noted that the melting point and density are both similar as expected. Furthermore, characterisation data such as NMR are provided in works such as those by Mascal et al. and Lakmini et al. [18,19]. According to Origin Chemicals, it is a white to dark brown chemical with slight solubility in water, where it decomposes [20]. Lately, this company has made significant commercialisation efforts for this chemical with a particular focus on its ready production from biomass [21].

Table 1. Properties of CMF and HMF.

| Name | 5-chloromethylfurfural (CMF) | 5-hydroxymethylfurfural (HMF) |
|--------------------------------------|---|---|
| Chemical structure |  |  |
| CAS number | 1623-88-7 | 67-47-0 |
| Canonical SMILES code | <chem>C1=C(OC(=C1)C=O)CCl</chem> | <chem>C1=C(OC(=C1)C=O)CO</chem> |
| Molecular formula | $C_6H_5ClO_2$ | $C_6H_6O_3$ |
| Molecular weight (g/mol) | 144.55 | 126.11 |
| Boiling point (°C) | 137–138 (P = 5 Torr) [22] | 350–354 (P = 760 Torr) [23] |
| Melting point (°C) | 37.8–38.6 [24] | 28–33 [23] |
| Relative density (g/mL) at T = 33 °C | 1.24 [20] | 1.24 [23] |

Sustained legislative requirements such as Registration, Evaluation, Authorization and Restriction of Chemicals (REACH EC 1907/2006) and Integrated Pollution Prevention and

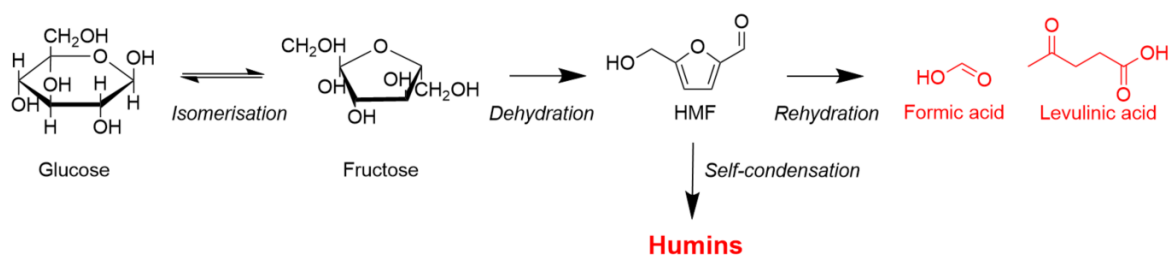
Control (IPPC, EC 1/2008) incentivise the selection of cleaner and sustainable production media [25,26]. This concept is further bolstered by green metrics, in which holistic process considerations, such as LCA and adherence to green chemistry principles, are of the utmost importance to the sustainable longevity of CMF production [27]. Consideration of the green metrics detailed by Sheldon could prove a useful comparative tool for scale-up processes for the production of CMF. Specifically, the metrics regarding the use of solvents in the production of both HMF and CMF excel in a biphasic system, and effective recycling and reuse of extraction media would greatly minimise the environmental footprint of these processes [28].

Since Mascal's perspective article in 2019, interest in the production of CMF and its synthesis has undergone a significant increase [16]. Here, we summarise some of the fundamental aspects of the production of CMF in parallel with HMF and furfural as well as the latest developments in this sense, including the possibility of using alternative solvents for the production. In addition, we present a compilation of the relevant value-added products that can be derived from CMF as a demonstration of the array of possibilities that it offers as building block for biorefineries. These products have a myriad of potential use cases, such as 2,5-dimethylfuran (DMF) as a biofuel candidate derived through hydrogenation of CMF. Furthermore, potential oxidation products of CMF are important polymeric building blocks, namely, FDCA and 2,5-furandicarbaldehyde.

2. Production of HMF and Furfural

Most commonly, the production of HMF and furfural through dehydration of hexose and pentose sugars, respectively, has taken place under acid-catalysed conditions in monophasic aqueous media.

The general reaction towards HMF is shown in Scheme 1, whereas Table 2 highlights some examples of studies where HMF is produced from saccharide feedstock, fructose and sucrose, and exhibits relatively low yields at 32% [29]. This low yield trend carries over to the more complex disaccharide substrates requiring hydrolysis to the fructose and glucose monomers before subsequent dehydration to HMF at a yield of 21% [30]. In both cases, these poor yields are attained despite the high feedstock conversions observed, which is indicative of how this approach leads to a very limited selectivity to HMF.

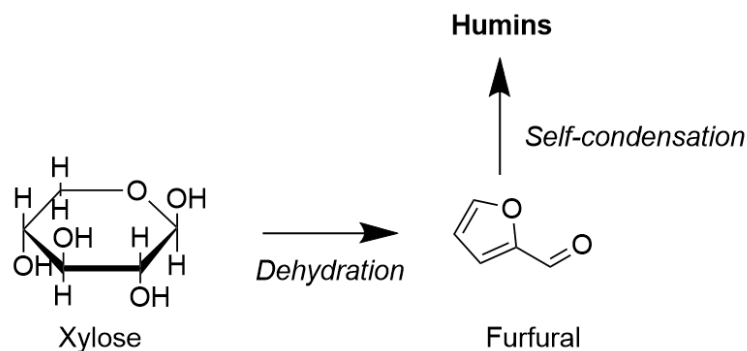


Scheme 1. Reaction pathway for the production of HMF from hexose sugars under acid-catalysed conditions in an aqueous medium.

Table 2. Selected examples of works on the monophasic production of HMF and furfural from biomass.

| HMF | | | | | | |
|------------------------------------|---|------------------|------------|--------------------------|-----------|------|
| Feedstock | Catalyst | Temperature (°C) | Time (min) | Feedstock Conversion (%) | Yield (%) | Ref. |
| Fructose 52 mM | HCl 1 M | 160 | 30 | 78 | 32 | [29] |
| Sucrose 0.5 M | H ₂ SO ₄ 0.5 M | 130 | 240 | 90 | 22 | [30] |
| Furfural | | | | | | |
| Xylose 52 mM | H ₂ SO ₄ 0.1 M | 200 | 4 | 98 | 65 | [31] |
| Corn cob 70.6 g·L ⁻¹ | PTSA 0.28 M | 165 | 48 | 96 | 75 | [32] |

Likewise, the production of furfural starting from xylose or complex raw materials like corn cob has been widely reported in monophasic aqueous media. In contrast to HMF, furfural synthesis utilising both monosaccharides and complex feedstocks observed a higher yield at 65% and 75%, respectively [31,32]. These improvements in yields can be attributed to the structure of furfural, where the lack of -OH moiety allows for a higher partition ratio that leads to less self-condensation to humins (Scheme 2), in addition to the impossibility of a rehydration reaction to LA and FA as in the case of HMF.



Scheme 2. Monophasic aqueous reaction pathway of xylose to furfural under acid-catalysed conditions.

As indicated in Schemes 1 and 2, the monophasic production of HMF and furfural is plagued with undesired side reactions resulting in limited yields and selectivity. Thus, biphasic reaction systems have been investigated as an alternative. Through this approach, reaction with *in situ* extraction can take place; this is presented as both a mitigation and intensification strategy for the production of furans from biobased substrates, as depicted in Figure 1. This hybrid unit operation combines reaction and separation by extraction into a single unit operation, which can also lead to significant capital and operating expenses upon scale-up, thus aligning with the philosophy of Process Intensification [33].

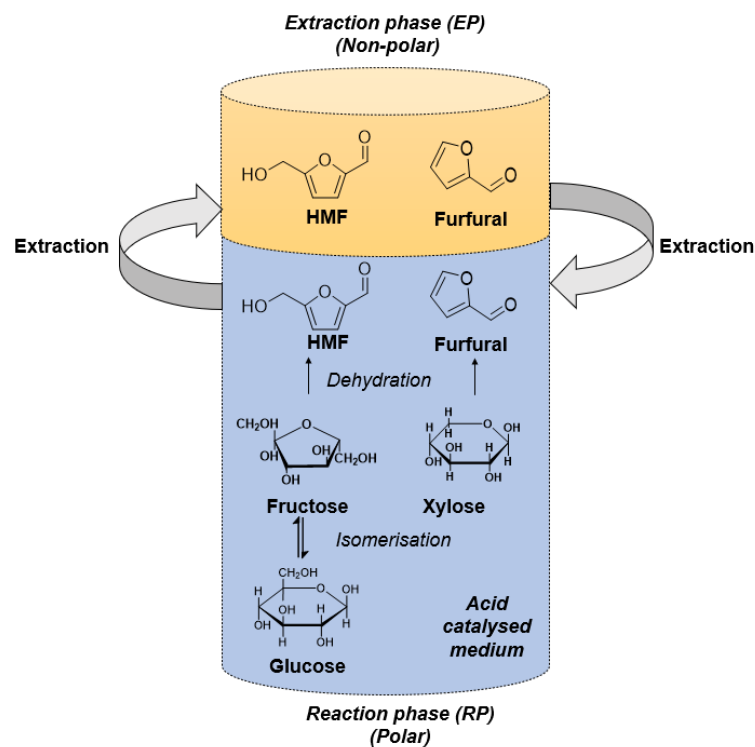


Figure 1. Biphasic production of HMF and furfural from hexose and pentose sugars, respectively, under acid-catalysed conditions.

Table 3 presents a selection of works detailing the biphasic production of HMF and furfural. With a broad body of literature available, these works showcase the range of solvents, feedstock, and some catalysts [8,34]. What is remarkable to observe is that yields of HMF as high as 78% and 81% were realised after relatively short reaction times of 10 and 16 min, respectively. These examples both used fructose, the simplest sugar, as feedstock, with gamma valerolactone (GVL) and methyl isobutyl ketone (MIBK) as extraction solvents [35,36]. Glucose is also a simple hexose monomer; however, isomerisation towards fructose must occur before further dehydration towards HMF, which accounts for the decreased yields of 40% reported with a tetrahydrofuran (THF) extraction solvent [37]. This isomerisation is driven by the Lewis acidity of the catalysts [30]. Finally, other starting materials like cellulose have been used as initial substrate. In the example provided, yields of 49% were obtained using $\text{FeCl}_3\text{-CuCl}_2$ as catalyst rather than other, simpler homogeneous catalysts [38].

Table 3. Selected examples of works on the biphasic production of HMF and Fur.

| HMF | | | | | | | |
|------------------------------------|---|--|------------------|------------|--------------------------|-----------|------|
| Feedstock | Polar/Non-Polar | Catalyst | Temperature (°C) | Time (min) | Feedstock Conversion (%) | Yield (%) | Ref. |
| Fructose 50 mM | H ₂ O/GVL 1/9 | HCl 10 mM | 100 | 10 | 90 | 78 | [35] |
| Cellulose 50 mM | H ₂ O (with NaCl)/1- butanol 1/1 | FeCl ₃ -CuCl ₂ 0.02 M | 190 | 45 | 91.3 | 49 | [38] |
| Fructose 0.5 M | H ₂ O/MIBK 1/4 | H ₂ SO ₄ 0.05 M | 155 | 16 | 96 | 81 | [36] |
| Glucose 25 mM | H ₂ O (with NaCl)/THF 1/3 | AlCl ₃ 25 mM | 140 | 90 | 90 | 40 | [37] |
| Furfural | | | | | | | |
| Corn cob 26.7 g·L ⁻¹ | Water/GVL 1/4 | H ₂ SO ₄ 10 mM | 190 | 20 | - | 99.5 | [39] |
| Arabinose 2 mM | H ₂ O/2-butanone 1/4 | [BMIM]Cl- AlCl ₃ 1:1 (IL ratio) | 140 | 30 | 100 | 60 | [40] |
| Xylose 0.25 mmol | [ChCl:OA]/MIBK 1/1 | AlCl ₃ ·6H ₂ O 0.125 mmol | 100 | 40 | 44.8 | 84.8 | [41] |
| Xylose 80 mM | H ₂ O/MIBK 1/1 | HCl 0.1 M | 170 | 30 | 93 | 85 | [42] |
| Xylan 14 mM | H ₂ O (with NaCl)/GVL 1/4 | Al ₂ (SO ₄) ₃ 10 mM | 160 | 30 | 99 | 87.8 | [43] |

Furfural production is also detailed in Table 3, with yields generally observed to be higher than those of HMF, which can be attributed to the enhanced partitioning between phases, limiting side reactions and hence also improving selectivity to the furan. A variety of feedstocks were presented for furfural production, such as arabinose, xylan, corn cob, and xylose. These selected articles include an array of catalysts, as is the case of ionic liquid (IL) [BMIM]Cl-AlCl₃, which highlights the emergence of alternative solvent types in these biphasic systems [40]. Furthermore, deep eutectic solvents (DES) have also been employed as a reaction medium, for example, the use of ChCl and oxalic acid (OA) in a molar ratio of 1:1, with MIBK serving as extraction phase. This system achieved a yield of 44.8% with around 84.8% conversion of the xylose substrates utilising AlCl₃·6H₂O as catalyst to pro-

vide the necessary Brønsted acidity [41]. In another example of biphasic furfural production, corn cob was used as starting material providing a yield of furfural of 99.5% with H_2SO_4 in just 20 min, although it is worthwhile to highlight the high temperature of 190 °C needed [39]. Finally, the yields from xylan and xylose substrates are similar, at 87.8% and 85%, respectively, although at a lower temperature of 130 °C for xylan as opposed to 170 °C for xylose, in correspondence with the higher complexity of the substrate, which requires its hydrolysis before dehydration [42,43].

3. Production of CMF

HMF presents issues with its ready rehydration to undesired by-products in aqueous reaction systems, which can occur to a significant extent considering the relatively limited extraction despite the use of biphasic systems for in situ extraction. This is undoubtedly a matter of concern in devising the large-scale implementation of the production of this chemical. For this reason, CMF is proposed as an HMF analogue chemical with enhanced partitioning from aqueous media due to the lack of -OH moiety and enhanced synthetic upgrading possibilities stemming from the -Cl leaving potential of the group [15]. CMF as a product in the context of the bioeconomy has been gaining momentum in the last years and significant progress is being made towards its cleaner production. Biphasic production of CMF, shown in Figure 2, can be detailed through the dehydration of hexose monomers under Brønsted acid-driven conditions followed by subsequent chlorination with a suitable chlorine donor, this being HCl in most cases [44].

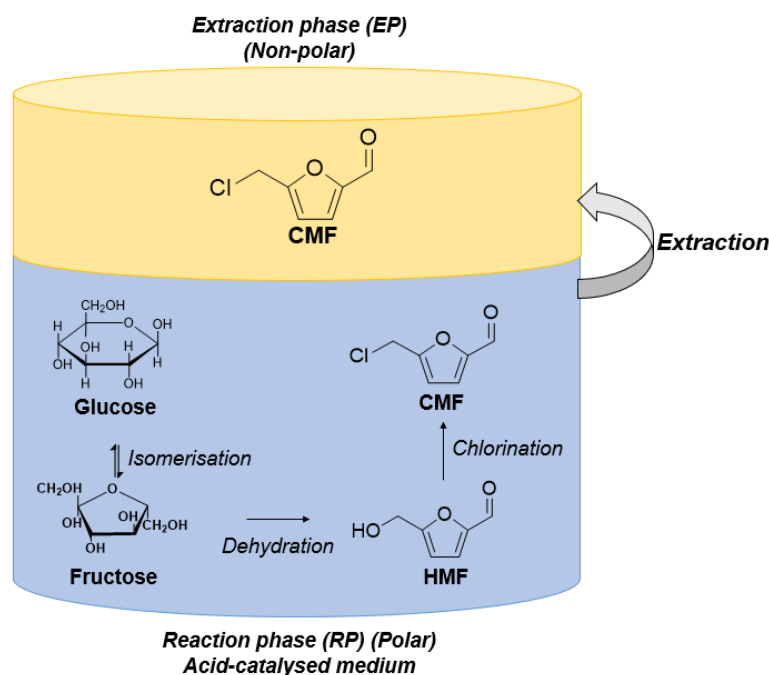
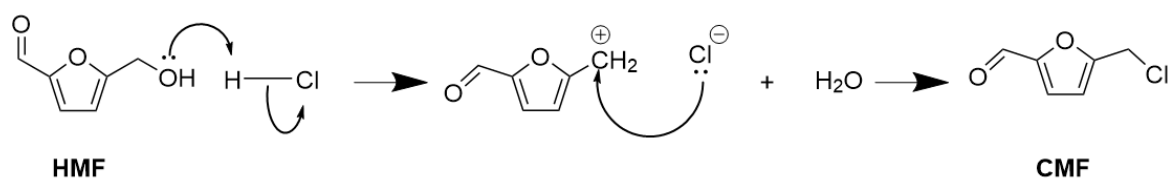


Figure 2. Biphasic reaction with in situ extraction of CMF from hexose monomers under acid-catalysed conditions.

The chlorination of HMF towards CMF is described in Scheme 3; this is an $\text{S}_{\text{N}}1$ mechanism in aqueous media. The exact location of the chlorination towards CMF, either occurring in the aqueous or organic phase, is still in contention. Mascial notes that evidence indicates that the latter may be more likely as the yields of CMF are tied to the partitioning of HMF into the organic phase [16].



Scheme 3. Chlorination of HMF towards CMF through S_N1 mechanism under acid-catalysed conditions in aqueous media.

3.1. CMF Production from Sugar Monomers and Dimers

The first mention of CMF as a target product was by Fenton et al. in 1901, wherein the production of this halogenated furan derivate was described through the addition of ether to levulose under the catalytic effect of HCl. This process yielded CMF in undisclosed amounts but started the development of halomethyl furfurals [17]. Table 4 details CMF synthesis from simple sugar monomers or dimers and is presented in chronological order to highlight the developments throughout recent years. The vast majority of systems use HCl in varying concentrations as the catalyst to promote the chlorination of CMF in addition to supplying the required Brønsted activity for sugar dehydration. Notable high yields were described from fructose at mild reaction conditions with yields of 80% through the use of CHCl₃ and dichloromethane (DCM) as an extraction solvent [45,46]. Furthermore, aqueous biphasic systems with toluene reported yields of 72% and 81.9% from fructose substrates at mild reaction temperatures of 65 °C and 80 °C, respectively [47,48]. The proliferous use of halogenated extraction solvents is aptly detailed with 1,2-dichloroethane (DCE) as the most commonly employed extraction solvent for the biphasic production of CMF, with other halogenated solvents such as DCM, chloroform, 1,1,2-trichloroethane (TCE), and tetrachloroethane (4CA) also being recurrent [19,46,49–51]. However, with green chemistry principles in mind, efforts have been made to steer away from halogenated extraction solvents, with alternatives such as toluene, anisole, and MIBK presented [52]. Two additional production methods with an HCl catalyst from fructose and a DCE extraction phase are detailed, with high yields reported at 71% and 85% [53,54]. Glucose as a starting feedstock delivers lower yields than those with fructose using the same catalyst (HCl) and DCE extraction phase. This reduction is attributed to the initial isomerisation of glucose to fructose monomers that must occur before subsequent dehydration steps can occur, with reported yields of 64%, 17%, and 38% [55–57].

Initial work has begun on researching the kinetic model of CMF production through hexose dehydration, with two major works detailing a batch method and a continuous system. The first of these methods, detailed by Antonyraj et al., described the production of CMF through the dehydration of glucose, with an HCl catalyst, and subsequent extraction with DCE yielding an activation energy of 31 kJ·mol⁻¹ for CMF formation [57]. The reaction pathway proposed additionally included the parallel reactions to LA, FA, and humins in addition to the isomerisation back towards HMF in both the aqueous and organic phases. Rojahn et al. presented a novel continuous method of CMF production with the catalytic activity of HCl, through a micro and milli-structured coiled flow inverter, wherein the results indicate that no discernible side products from CMF or HMF intermediates were formed [58]. The reported activation energy of CMF formation from HMF at 74 ± 25 kJ·mol⁻¹ was higher than the batch methodology; however, the benefits of highly selective production were present. Furthermore, this continuous method also utilised a green extraction solvent in the form of anisole rather than the typically halogenated DCE, which despite environmental benefits still leaves room for further identification of effective green solvents as an alternative.

Table 4. Summary of works on the production of CMF from sugar monomers or dimers in biphasic systems.

| Feedstock | Polar Phase/Non-Polar Phase | Catalyst | Temperature (°C) | Time (h) | CMF Yield (%) | Ref. |
|-------------------------------------|--|---|------------------|----------|---------------|------|
| Sucrose 0.12 M | H ₂ O/DCM 1/1 | HCl 32 wt.% | 100 | 0.04 | 51 | [46] |
| Fructose 0.12 M | H ₂ O/DCM 1/1 | HCl 32 wt.% | 100 | 0.04 | 80 | [46] |
| Glucose 0.12 M | H ₂ O/DCM 1/1 | HCl 32 wt.% | 100 | 0.04 | 15 | [46] |
| Fructose 0.132 M | H ₂ O (with LiCl)/Toluene 10.5 g·L ⁻¹ | HCl 32 wt.% | 65 | 3 | 72 | [47] |
| Fructose 0.17 M | H ₂ O/DCE 1/2 | HCl (Conc.) | 80 | 0.25 | 71 | [53] |
| Fructose 0.005 M | H ₂ O/CHCl ₃ 1/3 | HCl (25 wt.%) | 45 | 10 | 80 | [45] |
| Fructose 33.3 g·L ⁻¹ | H ₂ O/DCE 1/2 | HCl 37 wt.% | 70 | 0.16 | 85 | [54] |
| Fructose 0.005 M | [ChCl:fructose (1:5)]/MIBK 1/10 | AlCl ₃ ·6H ₂ O 0.005 M | 120 | 5 | 50.3 | [52] |
| Sucrose 0.005 M | [ChCl:fructose (1:5)]/MIBK 1/10 | AlCl ₃ ·6H ₂ O 0.005 M | 120 | 5 | 17.8 | [52] |
| Glucose 1.5 M | H ₂ O/4CA | HCl 6 M | 110 | 1 | 29 | [49] |
| High-fructose corn syrup 37 wt.% | H ₂ O/DCM 2/3 | HCl 37 wt.% | 100 | 0.32 | 85 | [51] |
| Glucose 2.1 wt.% | H ₂ O/DCE 1/2 | BTBAC 0.2 wt.% | 90 | 3 | 64 | [55] |
| Glucose and xylose 5 wt.% | H ₂ O/DCE 1/2 | BTBAC 0.05 wt.% | 100 | 3 | 17 | [56] |
| Fructose 1 wt.% | H ₂ O/Toluene 1/2 | HCl 37 wt.% | 80 | 4 | 81.9 | [48] |
| Sucrose 1 wt.% | H ₂ O/Toluene 1/2 | HCl 37 wt.% | 100 | 4 | 70.2 | [48] |

| | | | | | | |
|----------------------------------|-----------------------------|--|-----|------|----|------|
| Fructose 0.002 M | [ChCl:OA (5:6)]/DCE 1/2 | AlCl ₃ ·6H ₂ O hydrolyses to HCl 0.015 M | 120 | 0.5 | 86 | [59] |
| Sucrose 0.002 M | [ChCl:OA (5:6)]/DCE 1/2 | AlCl ₃ ·6H ₂ O hydrolyses to HCl 0.015 M | 120 | 0.5 | 80 | [59] |
| Glucose 0.05 M | H ₂ O/DCE 1/2 | HCl 37.2 mmol | 80 | 2 | 38 | [57] |
| Fructose 10 g·L ⁻¹ | H ₂ O/anisole | HCl 26% | 90 | 0.07 | 79 | [58] |

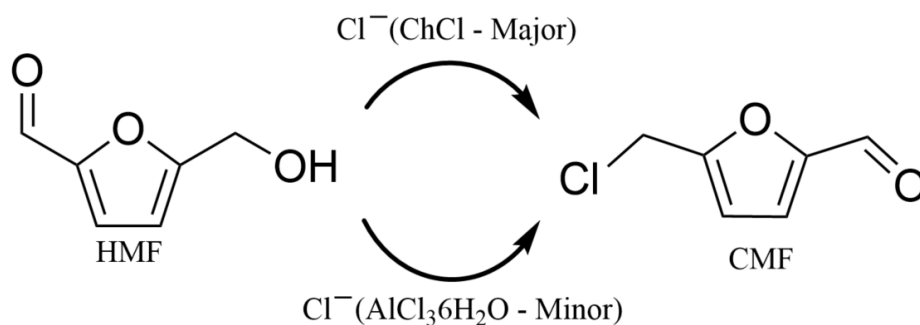
3.2. CMF Production from Real Biomass Sources

Economically viable process development will require the use of real biomass rather than sugar monomers for the production of platform chemicals in a biorefinery context. Table 5 provides an overview of the development of CMF processes in which biomass is utilised as the initial feedstock. In the new century, Mascall et al. presented an initial method of CMF production through the dehydration of microcrystalline cellulose under concentrated HCl as catalyst in an aqueous medium and 1,2-dichloroethane (DCE) as extractive phase. The aqueous phase included LiCl as additive to promote a salting-out effect and hence enhance the migration of CMF to the organic phase [18]. However, this process required long reaction times at 30 h and large amounts of solvents. For this reason, it was subsequently refined through an increase in temperature from 65 °C to 100 °C and the removal of LiCl. These changes decreased the reaction time to 2 h, decreased the aqueous to organic ratio from 1:5.5 to 1:2, and increased the yield to 84% from 71% [60]. As can be seen, further advancements were made after Mascall et al.'s efforts in 2008 [18] and 2009 [60], through a focus on decreasing the reaction times and changes of initial substrate such as eucalyptus kraft pulp, Norway spruce softwood, eucalyptus hardwood, palmarosa, lemon grass, and citronella grass [61,62]. High lignin content in complex biomass is a significant issue and generally hinders biobased chemical production from carbohydrate bases. This can be seen from the relatively low yields of eucalyptus kraft pulp, Norway spruce softwood, and eucalyptus hardwood at 21.3%, 33.7%, and 47.4% [61]. Further complex biomass such as corn stover and sugarcane bagasse exhibited good yields of 63% and 80%, respectively, with DCE as an extraction solvent and HCl as catalyst [63,64]. Bhat et al. detailed the use of microcrystalline cellulose as feedstock using ZnCl₂ as a catalyst, which partially solubilized the cellulose, suppressing side reactions to achieve a reasonable yield of 72% [65].

In an effort to address the circular economy and the valorisation of food waste by-products, additional efforts have been made using rice-based food waste as a local sustainable starting material, which could help mitigate the overall negative footprint of a CMF production process. A simple methodology describing the use of four types of rice waste was detailed, wherein 4 wt.% of rice bran, rice hull, broken white rice, and immature brown rice were added to a glass vessel containing 32% HCl and chloroform as extraction solvent. In this process, the reaction was heated at 100 °C for two hours and the corresponding CMF-rich oil was extracted and analysed providing yields of 22.7, 29.6, 52.2, and 48%, respectively [19]. A continuous method of production with a coiled flow inverter reactor was presented in which anisole, a green solvent, was fed continuously to produce CMF at a yield of 79% at a residence time of 256 s [58]. The highest CMF yield (96.70%) was reported by Moron et al. under low temperature and ambient pressure conditions from initial hydrolysis of aspen wood chips followed by downstream saccharification [66].

In general, from this account it is obvious that homogeneous catalysts have been used for the conversion to CMF, with a clear prevalence of HCl and AlCl₃. Their function in this case is not only to provide acidity to the medium for the reaction mechanism to take place, but also to act as chlorine donors to form CMF. In this sense, it is worthwhile to remark that DES can be employed as reaction phase, where ChCl can act as Cl donor in addition to the fact that using this polar medium instead of water as reaction phase helps to mitigate the progress of the production of humins and the rehydration of the intermediate HMF species to levulinic acid and formic acid. One example of this is the use of ChCl:fructose (1:5) or different combinations of ChCl as hydrogen bond acceptor (HBA) with hydrogen bond donors (HBD) in different ratios, such as inulin and sucrose, providing yields of 50.3%, 22.6%, and 17.6%, respectively [52]. Further investigations of alternative DES have been made wherein ternary solvents were tested. In this effort, different combinations of ChCl were tested, first with different organic acids such as oxalic acid (OA), and malic, citric, formic, succinic, and acetic acid. Subsequently, a series of chlorine salts were

combined with ChCl and OA, with $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ outperforming the rest, indicating a ChCl:OA: $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ (12.5:15:2) DES as the optimal reaction phase. This DES was reported to hydrolyse to create the Brønsted acidity for dehydration to CMF. Reported results indicate excellent yields of 86% and 80% from fructose and sucrose as substrates, respectively [59]. In that work, Chen et al. also present a potential reaction mechanism for the chlorination of the HMF intermediate formed, shown in Scheme 4, wherein it is suggested that the two DES constituents containing Cl behave as donors to different extents.



Scheme 4. Proposed HMF halogenation towards CMF using DES, adapted from Chen et al. [59].

This plausible mechanism suggests that the major chlorine source is the HBA component of the DES, in this case, the ChCl. This presents the possibility of CMF production without the addition of concentrated HCl as production processes currently use, with the subsequent potential avoidance of the use of this highly corrosive compound. However, this brings into question the viability of working with DES due to its high viscosity and difficult regeneration if degraded by excess water produced through dehydration. In addition, the self-consuming system, ChCl:OA (5:6), will require some form of chlorine replacement to ensure continued functionality.

Finally, with an eye towards the kinetics of CMF production from biomass, Barman et al. present an energy-efficient and eco-friendly UV-ultrasonic synthesis of CMF from soluble starch using a continuous flow-packed bed reactor using a smopex-101 and TiO_2 catalyst, with the first heterogeneous kinetics reported. The developed kinetic model formulated revealed activation energies for the soluble starch hydrolysis, glucose dehydration, and principally the chlorination of HMF at values of 79.04, 61.55, and 52.20 $\text{kJ} \cdot \text{mol}^{-1}$, respectively. This study additionally utilised an LCA to identify cyclohexane as an extraction solvent in conjunction with the smopex-101 and TiO_2 dual catalytic system to achieve CMF purity approaching 96% [67].

Considering the current lack of works reporting kinetic models to describe the production of CMF both from simple and more complex feedstock, the generation of further models under different conditions and different catalysts is an area that needs further development. These studies are crucial for subsequent reactor design as well as process design and simulation and their subsequent techno-economic analysis, which will help determine the viability of process implementation.

Table 5. Summary of works on the production of CMF from biomass, where ^a refers to wt.% of the polar phase.

| Feedstock | Polar Phase/Non-Polar Phase | Catalyst | Temperature (°C) | Time (h) | CMF Yield (%) | Ref. |
|---|---|---|------------------|----------|---------------|------|
| Microcrystalline cellulose 1.4 wt.% ^a | H ₂ O (with LiCl)/DCE 1.5/5 | HCl (Conc.) | 65 | 30 | 71 | [18] |
| Microcrystalline cellulose 1 wt.% ^a | H ₂ O//DCE 1/2 | HCl (Conc.) | 100 | 2 | 84 | [60] |
| Eucalyptus kraft pulp 0.02 wt.% ^a | H ₂ O/CHCl ₃ 4/5 | H ₃ PO ₄ 85 wt.% | 45 | 20 | 21.3 | [61] |
| Norway spruce softwood 0.02 wt.% ^a | H ₂ O/CHCl ₃ 4/5 | H ₃ PO ₄ 85 wt.% | 45 | 20 | 33.7 | [61] |
| Eucalyptus hardwood 0.02 wt.% ^a | H ₂ O/CHCl ₃ 4/5 | H ₃ PO ₄ 85 wt.% | 45 | 20 | 47.4 | [61] |
| Cellulose 16.7 g·L ⁻¹ | H ₂ O/TCE 1/1 | HCl 37 wt.% | 90 | 1 | 70 | [50] |
| Agarose 16.7 g·L ⁻¹ | H ₂ O/TCE 1/1 | HCl 37 wt.% | 90 | 1 | 54 | [50] |
| Rice straw 16.7 g·L ⁻¹ | H ₂ O/TCE 1/1 | HCl 37 wt.% | 90 | 1 | 57 | [50] |
| Barley straw 16.7 g·L ⁻¹ | H ₂ O/TCE 1/1 | HCl 37 wt.% | 90 | 1 | 68 | [50] |
| Wheat straw 16.7 g·L ⁻¹ | H ₂ O/TCE 1/1 | HCl 37 wt.% | 90 | 1 | 61 | [50] |
| Triticale 16.7 g·L ⁻¹ | H ₂ O/TCE 1/1 | HCl 37 wt.% | 90 | 1 | 59 | [50] |
| Rape stem 16.7 g·L ⁻¹ | H ₂ O/TCE 1/1 | HCl 37 wt.% | 90 | 1 | 53 | [50] |
| Grass (<i>Miscanthus sinensis</i> var. <i>purpurascens</i>) 16.7 g·L ⁻¹ | H ₂ O/TCE 1/1 | HCl 37 wt.% | 90 | 1 | 58 | [50] |
| Reed (<i>Phragmites communis</i> , Trin.) 16.7 g·L ⁻¹ | H ₂ O/TCE 1/1 | HCl 37 wt.% | 90 | 1 | 59 | [50] |
| Paper 16.7 g·L ⁻¹ | H ₂ O/TCE 1/1 | HCl 37 wt.% | 90 | 1 | 51 | [50] |
| Fibreboard 16.7 g·L ⁻¹ | H ₂ O/TCE 1/1 | HCl 37 wt.% | 90 | 1 | 42 | [50] |
| Inulin 0.005 M | [ChCl:fructose (1:5)]/MIBK 1/10 | AlCl ₃ ·6H ₂ O 0.005 M | 120 | 5 | 22.6 | [52] |
| Sugarcane bagasse 1 wt.% | H ₂ O/DCE 1/2 | HCl 37 wt.% | 90 | 3 | 81.9 | [64] |
| Corn stover | H ₂ O/DCE | HCl | 100 | 2 | 63 | [63] |

| | | | | | | |
|--|---|--|-----|-----|-------|------|
| 10 wt.% Palmarosa | 1/2 H ₂ O (with NaCl)/CHCl ₃ | 37 wt.% HCl | 100 | 1 | 76.5 | [62] |
| 20 wt.% ^a Lemon grass | 1/3 H ₂ O (with NaCl)/CHCl ₃ | 37 wt.% HCl | 100 | 1 | 72.4 | [62] |
| 20 wt.% ^a Citronella grass | 1/3 H ₂ O (with NaCl)/CHCl ₃ | 37 wt.% HCl | 100 | 1 | 65.8 | [62] |
| 20 wt.% ^a Cellulose | 1/3 [ChCl:OA (5:6)]/DCE | 37 wt.% AlCl ₃ ·6H ₂ O hydrolyses to HCl | 120 | 0.5 | 30 | [59] |
| 0.002 M Bamboo | 1/2 [ChCl:OA (5:6)]/DCE | 0.015 M AlCl ₃ ·6H ₂ O hydrolyses to HCl | 120 | 0.5 | 29 | [59] |
| 0.002 M Bamboo pulp | 1/2 [ChCl:OA (5:6)]/DCE | 0.015 M AlCl ₃ ·6H ₂ O hydrolyses to HCl | 120 | 0.5 | 35 | [59] |
| Microcrystalline cellulose | H ₂ O/DCE | ZnCl ₂ | 80 | 2 | 72 | [65] |
| 1.7 wt.% Rice Bran | 2/3 H ₂ O/CHCl ₃ | 3.4 wt.% HCl | 100 | 2 | 22.7 | [19] |
| 4 wt.% Rice hull | 1/4 H ₂ O/CHCl ₃ | 32% HCl | 100 | 2 | 29.6 | [19] |
| 4 wt.% Broken white rice | 1/4 H ₂ O/CHCl ₃ | 32% HCl | 100 | 2 | 52.2 | [19] |
| 4 wt.% Immature brown rice | 1/4 H ₂ O/CHCl ₃ | 32% HCl | 100 | 2 | 48 | [19] |
| 4 wt.% Soluble starch | 1/4 H ₂ O/CHCl ₃ | 32% HCl | 100 | 2 | 48 | [19] |
| 20 g·L ⁻¹ Glucose hydrolysate derived from Aspen wood chips | H ₂ O/cyclohexane 1/1.5 | Smopex-101 and TiO ₂ :ChCl 0.1 g | 80 | 1 | 58.75 | [67] |
| (3.03 wt.% glucose, 0.07 wt.% mannose, 0.090 wt.% xylose) | H ₂ O/chlorobenzene 1/2 | HCl | 90 | 2 | 96.70 | [66] |

3.3. Considerations and Tools for Solvent Selection in the Biphasic Production of CMF and Other Furans

Solvent selection in the context of biorefineries remains crucial in the development of cleaner effective biphasic systems, wherein a balance must be struck between the extractive capability and the environmental and health and safety (EHS) profile of the solvent. Concerning the latter aspect, several solvent selection guides have been proposed throughout the years, with the CHEM21 guide providing a valuable tool to assess their profile based on physicochemical properties (e.g., flash or boiling points) as well as regulatory (REACH) and global harmonized systems hazard statements [68]. As for extraction capability, a method for screening potential solvent candidates is the use of Hansen solubility parameters (HSPs). These HSPs consist of three major terms, δ_D for dispersion, δ_P for polarity of the dipole moment, and δ_H for hydrogen bonding [69]. Lane et al. present the HSPs of a range of solvents, here presented in Figure 3, to which we have added the HSPs of CMF and H₂O. These CMF values were calculated using Hansen Solubility Parameters in Practice (HSPiP) software, version 5.4.08. The solvents present are as follows, tetrachloroethane 4CA, DCM, TCE, toluene (Tol), DCE, and perchloroethylene (PCE) [49]. It can be seen that the dominating HSP in water is δ_H , which follows due to the nature of the molecule, wherein this is largely different to the δ_H of both the organic solvents and CMF, indicating a degree of immiscibility between the polar and non-polar phase.

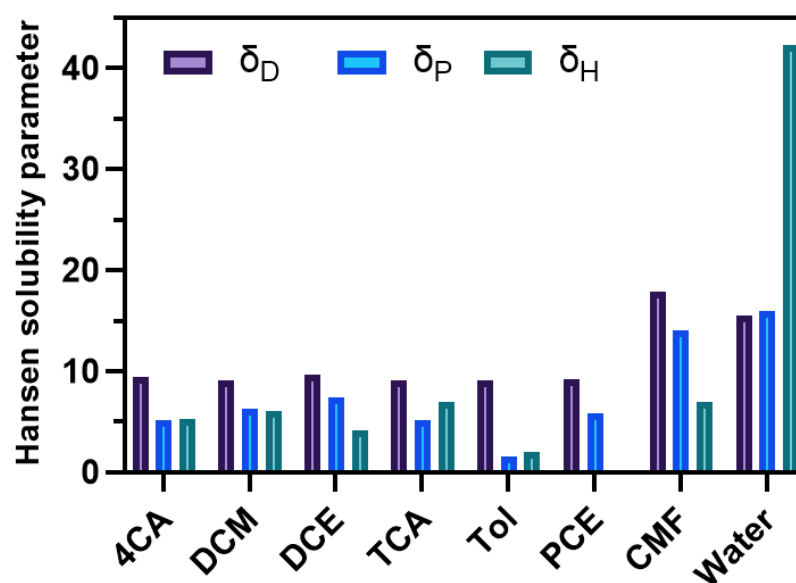


Figure 3. HSP for CMF and a selection of solvents, adapted from Lane et al. with the addition of calculated CMF HSP [49,70].

The advantage of using HSP calculations allows for the identification of effective solvents for CMF solubility through the prediction of the likelihood of CMF solubility in both the reaction and extraction phases. These works coupled with descriptions of mild reaction conditions and low-toxicity reagents and solvents allow for the development of truly green processes. An additional measure that could be utilised for effective solvent screenings for CMF is the COnductor-like Screening MOdel for Real Solvents (COSMO-RS) [71]. This semi-quantitative quantum chemistry approach has already seen successful implementation for both HMF and furfural solvent screenings [34], and as such could likewise be used for screenings with CMF. The advantage of this computational approach hinges on the ease of rapid large-scale screenings for prediction of partition coefficients, identifying effective solvents to then be experimentally validated. Figure 4 presents σ -profiles, or probabilistic charge distributions of three common extraction solvents, MIBK, DCE,

and DCM, for solutes HMF, CMF, and furfural, and H₂O as the solvent from which extraction would take place. Additionally, the COSMO-RS-generated charge surfaces are also provided, allowing for simple identification of matching regions for both HBD and HBA regions, alongside the non-polar region. In general, as in the “like-dissolves-like” rule, the more similar the σ -profiles between different compounds, the higher the likelihood of interaction between them and hence their mutual solubility. These σ -profiles can be used for the calculation of chemical potentials and the latter can be employed to determine fluid phase equilibria among others [71].

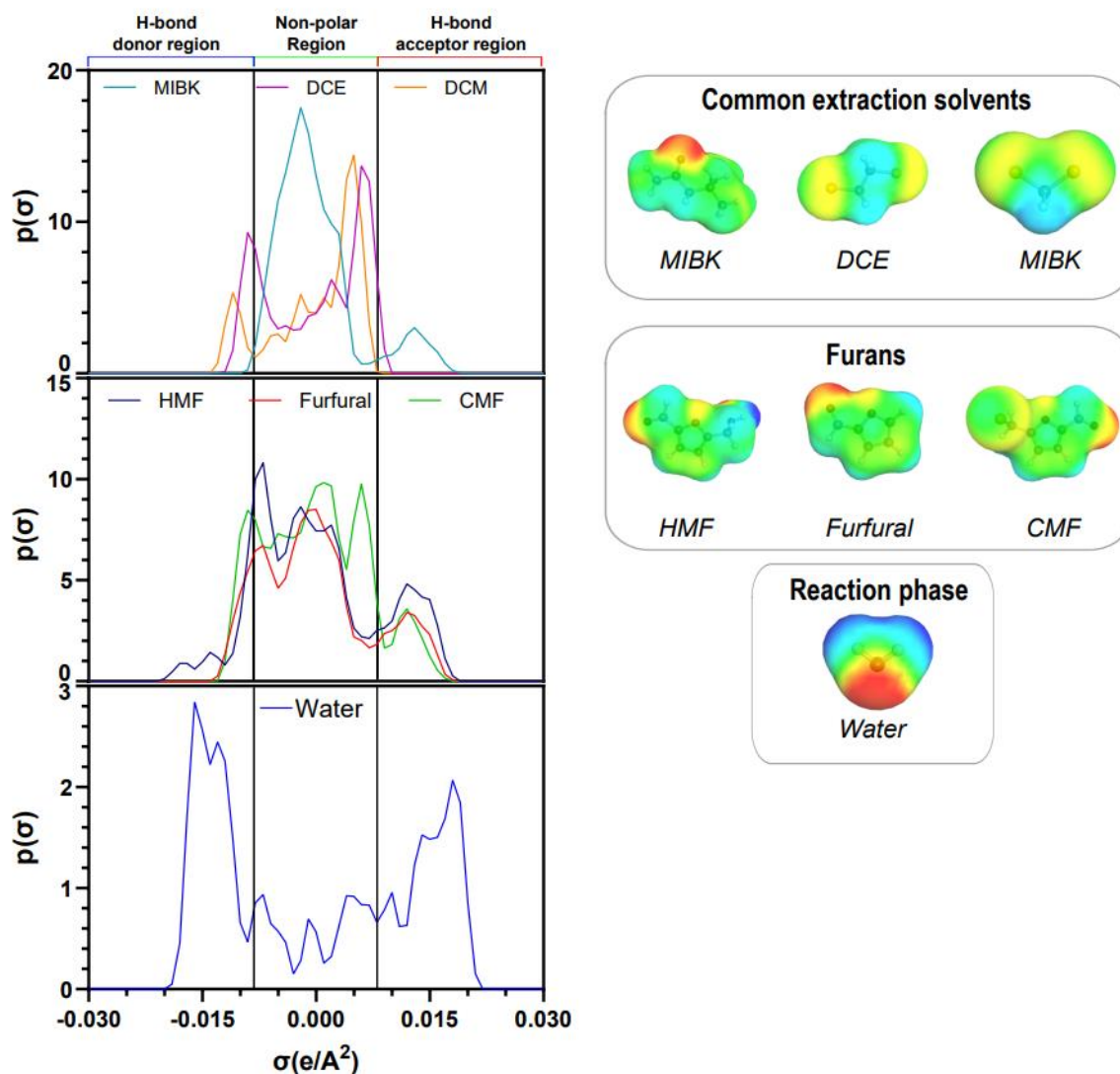


Figure 4. σ -profiles and COSMO surfaces of three commonly used extraction solvents (MIBK, DCE, and DCM) alongside HMF, furfural, and CMF of the lowest energy (c0) conformers.

4. Overview of the Synthetic Possibilities of CMF

The vast array of potential derivatives from CMF is one of the main attractions of this halogenated HMF analogue as a biobased platform chemical building block. Although CMF is unsuitable as a direct-use monomer, synthetic upgrading under various conditions allows for final-stage use as biofuels, herbicides, and pharmaceutical precursors, among others [72–74]. This section is dedicated to the common one-step or one-pot reactions of CMF to a target derivative. Figure 5 provides a brief overview of the numerous reaction pathways available for the synthetic upgrading of CMF, among which are rehydration, hydrogenation, oxidation, esterification, etherification, amination, and others.

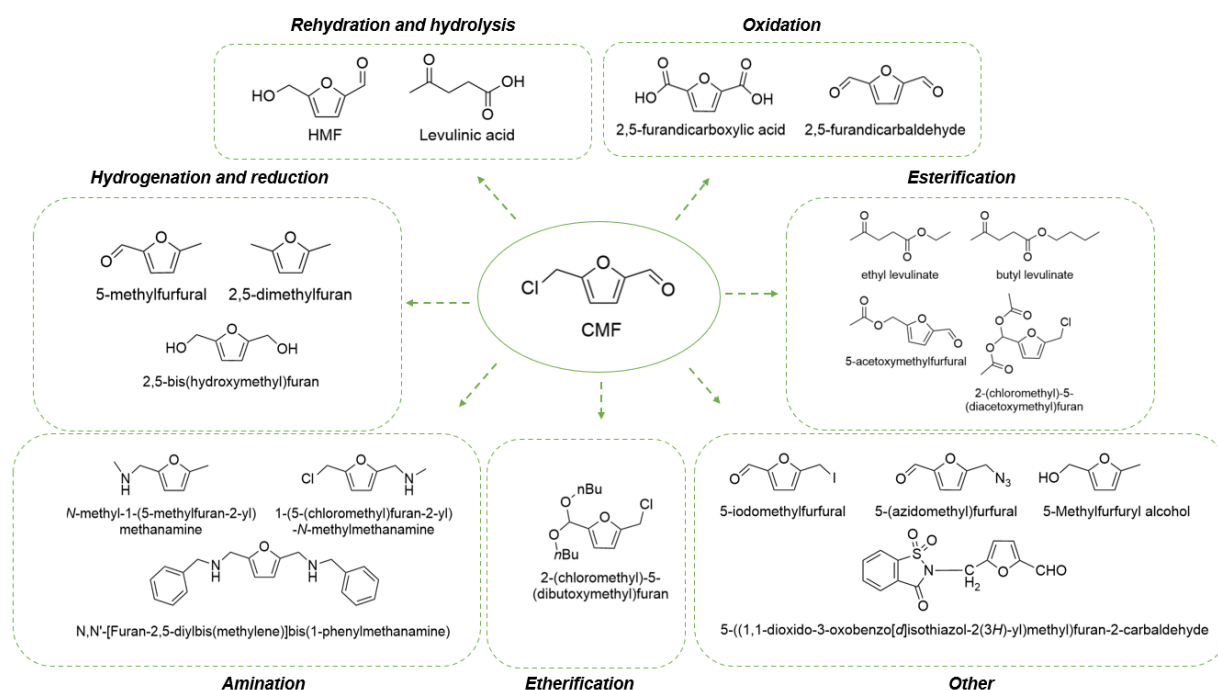
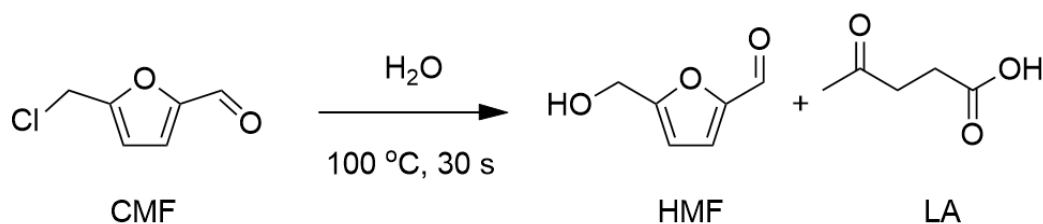


Figure 5. CMF as a platform chemical candidate.

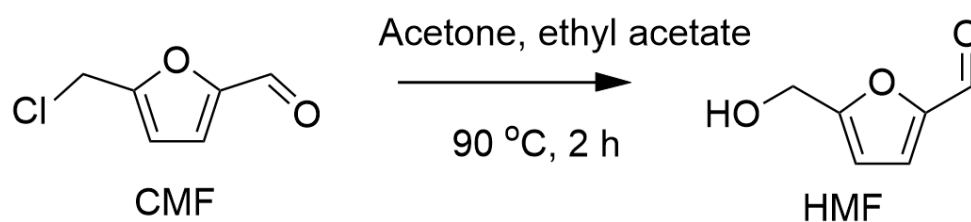
4.1. Rehydration and Hydrolysis

Discussion of CMF rehydration to HMF and LA (Scheme 5) is imperative due to the relative ease of reaction through mild conditions. Mascari et al. report a high molar yield of HMF (86%) with a comparatively low LA yield of (10%) at 100 °C after 30 s [75]. This reaction was undertaken in the absence of a catalyst and performed remarkably well at such short reaction times. Continuous rehydration processes have been additionally described with the formation of HMF through a continuous flow device operating at 100 °C and a residence time of only 2.5 min. This system leveraged the flow of a continuous aqueous phase with interspersed organic extraction media THF to act as a biphasic system with moderate HMF selectivity of 71% with an accompanying 20% presence of LA [46].



Scheme 5. Rehydration products of CMF towards HMF and LA [75].

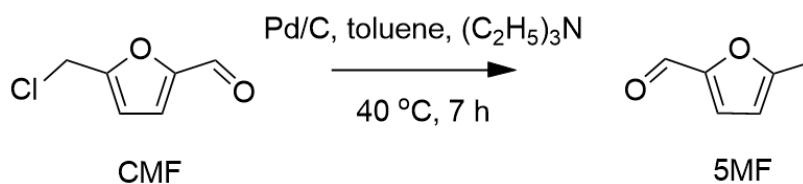
Hydrolysis of CMF to HMF was reported with a reasonable molar yield of 72% at 100 °C under continuous flow conditions with a space-time of 1 min using 4 wt.% CMF in acetone solution and subsequently extracted with ethyl acetate (Scheme 6) [76]. This HMF product was then utilised through further hydrogenation to 2,5-bis(hydroxymethyl)furan, a precursor for polymeric materials and resins.



Scheme 6. CMF hydrolysis followed by extraction with ethyl acetate [76].

4.2. Hydrogenation and Reduction

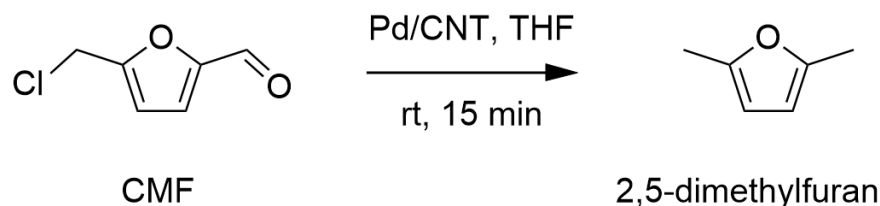
Catalytic hydrogenation of CMF leads to the formation of DMF which is an exciting single-monomer biofuel candidate, with the advantages of removing the need to retrofit conventional internal combustion engines and minimising the production of water as seen with other biofuel additives like ethanol. Furthermore, the energy value of DMF is similar to that of both petrol and diesel at $31.5 \text{ MJ}\cdot\text{L}^{-1}$, $31.9 \text{ MJ}\cdot\text{L}^{-1}$, and $34.9 \text{ MJ}\cdot\text{L}^{-1}$, respectively [15,77]. DMF synthesis typically occurs through the intermediate generation of 5-methylfurfural (5MF), which can also be isolated for use as a food additive or synthetic intermediate [78]. Scheme 7 presents the synthesis of 5MF from CMF through the use of a Pd/C, toluene, and $(\text{C}_2\text{H}_5)_3\text{N}$ at 40°C for 7 h, which realised a yield of 97% with an initial 6.92 mmol CMF [79].



Scheme 7. Hydrogenation of CMF to 5MF [79].

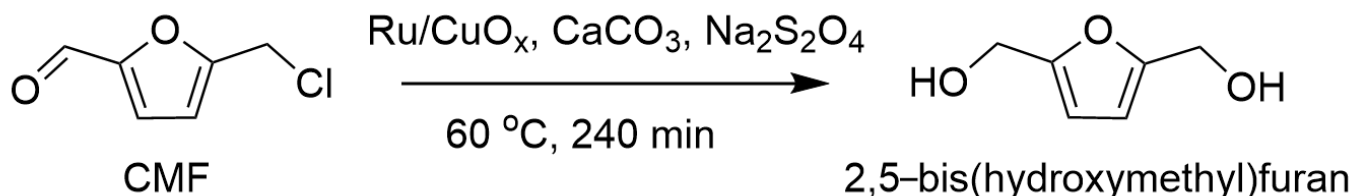
A high yield of 5MF was also achieved (91%) in an H_2O /toluene biphasic system under mild conditions again using a Pd/C catalyst [80]. This biphasic system was used as this synthesis was part of a series of steps required to synthesise DMF. Additionally, in a different approach, Lund et al. presented the use of electrochemical cells to initiate the reduction of furans, specifically HMF and CMF, towards 5MF in a single unit. An electrochemical system was used with a mercury pool cathode and two-phase cathode consisting of an organic phase (75% DCE and 25% diethyl ether) and an aqueous phase (125 mL 6 M HCl, 1 M NaI). This was operated at 20°C for 20 h and provided around 50% yield of 5MF [81]. Alternatively, hydrogenation of CMF under mild conditions (40°C , 4 h) with a PdCl_2 catalyst could reach yields up to 88% [18].

The production of DMF under mild conditions via a catalytic hydrogenation route is presented in Scheme 8. The hydrogenation of CMF with a Pd/carbon nanotube (CNT) catalyst allowed for in situ generation of the acidic species required for high selectivity towards DMF at room temperature in a THF- H_2O media for 15 min, resulting in a yield of 92% [82]. Additionally, the hydrogenation of CMF with a Pd/C catalyst with cyclohexene extraction solvent at 60°C for 8 h displayed a molar yield of 88% [79]. Finally, Li et al. reported the heterogeneous dechlorination of CMF towards DMF leveraging the Pd-catalysed hydrosilane-mediated hydrodeoxygenation of the initial furanic material. This leads to a 72% overall yield towards DMF exclusively at 25°C and 70 min [83].



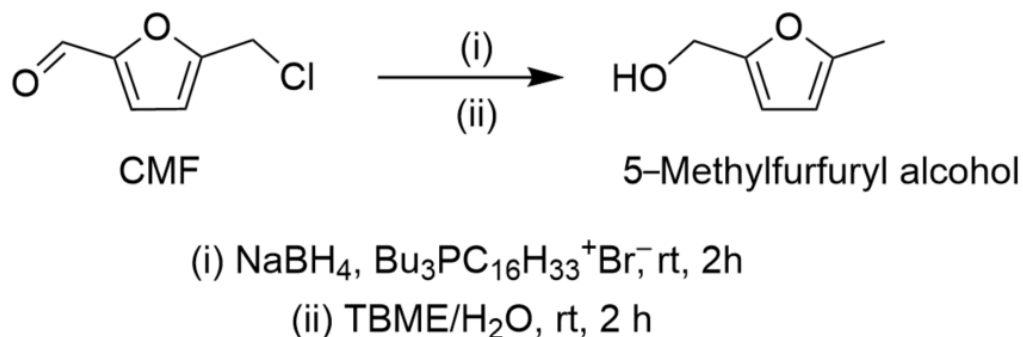
Scheme 8. Catalytic hydrogenation of CMF to DMF under mild conditions [82].

Scheme 9 describes the one-pot synthesis of 2,5-bis(hydroxymethyl)furan, where a 91% yield was realised using a Ru/CuO_x catalyst. This process involved hydrolysis of CMF to HMF and then subsequent hydrogenation in a one-pot system at 60 °C for 240 min [84]. Additionally, variations of base additives were investigated with the addition of CaCO₃ proving a yield of 76% of 2,5-bis(hydroxymethyl)furan with only a 13% HMF yield and a 3% yield of 2,5-bis(hydroxymethyl)tetrahydrofuran at >99% CMF conversion.



Scheme 9. One-pot reaction of CMF to BHMF via the intermediate hydrolysis to HMF [84].

Scheme 10 presents the formation of 5-methylfurfural alcohol; this reduction reaction sees the utilisation of phase transfer conditions to generate a yield of 73% in a two-step process [46]. The first stage involves the use of sodium borohydride and tributyl hexadecyl phosphonium bromide at room temperature for 2 h. The following stage then involves the addition of tert-butyl methyl ether and vigorous mixing followed by the separation of layers and evaporation and filtration of the organic layers post-drying with MgSO₄. Furthermore, this highlights a method of producing the same products of hydrogenation through reduction without the need for the addition of H₂.

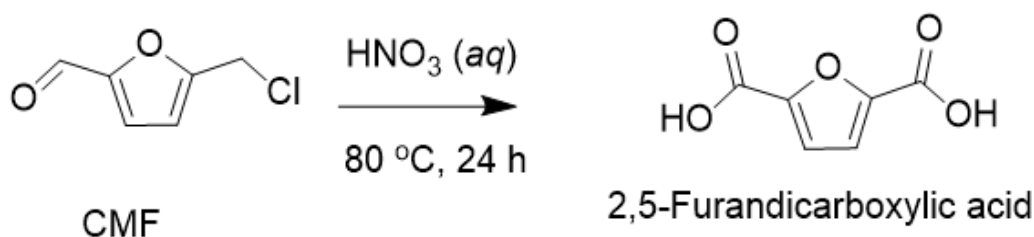


Scheme 10. CMF to 5-methylfurfuryl alcohol through reduction under phase transfer conditions [46].

4.3. Oxidation

CMF has been reported as a starting material to undergo oxidation to different degrees. In this sense, acid-driven oxidation of CMF yields two major products, FDCA and

2,5-furandicarbaldehyde, both of which are highly praised building blocks in synthetic chemistry. Owing to the bifunctionalised structure around the furan ring, FDCA is a promising platform chemical candidate with already widespread use in the production of polyethylenefuranoate, a biobased polymer with promise as an alternative to polyethylene terephthalate (PET) [85]. Production of FDCA through CMF oxidation, as shown in Scheme 11, was reported by Brasholtz et al. in a batch system containing aqueous nitric acid, wherein a sparse yield of 59% was reported at 80 °C for 24 h [46].



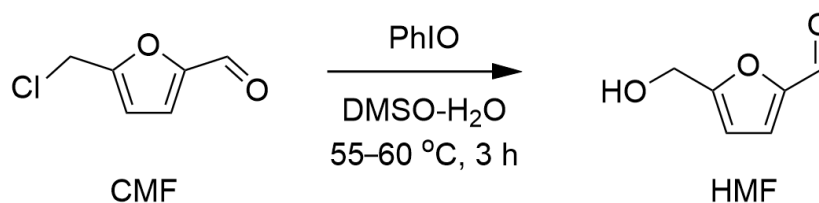
Scheme 11. Oxidation of CMF to a dicarboxylic acid derivate, FDCA [46].

Aside from FDCA, 2,5-furandicarbaldehyde is another synthetic building block of interest that can also be formed through the oxidation of CMF as seen in Scheme 12. The partial oxidation of CMF to 2,5-furandicarbaldehyde was first detailed in 1912 through the use of nitric acid for 45 min, with the product subsequently being extracted by chloroform [86]. More recent developments improving the yield use dimethyl sulfoxide (DMSO) to initiate the oxidation at 150 °C for 18 h at a yield of 81%, as shown in Scheme 12 [87].



Scheme 12. Oxidation of CMF to 2,5-furandicarbaldehyde [87].

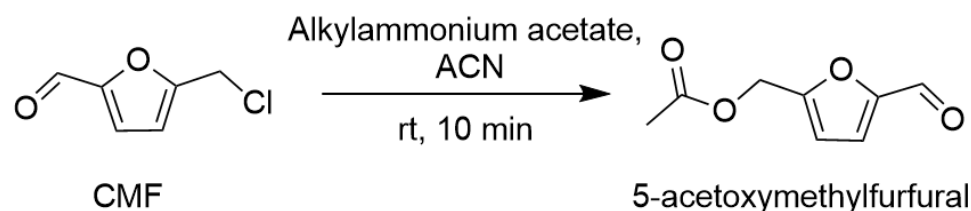
Finally, a hypervalent iodine reagent, specifically iodosylbenzene (PhIO), was used for the oxidation of CMF to HMF using DMSO-H₂O as reacting medium, where a yield of 90% was observed (Scheme 13) in a one-pot system at 55–60 °C for 3 h [62]. DMSO as a purely anhydrous reaction mixture failed to yield HMF even after 24 h, highlighting the necessity of water for successful HMF synthesis. The high oxidative capability of PhIO and the high polarity of DMSO ensured that mild conditions could be used to effectively produce HMF [62].



Scheme 13. CMF oxidation to HMF with hypervalent iodosylbenzene [62].

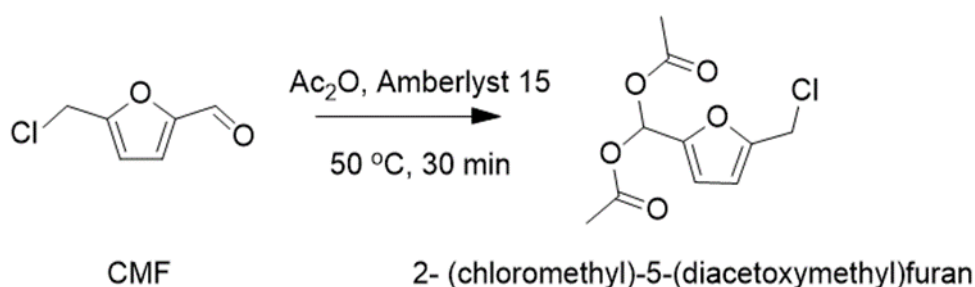
4.4. Esterification

Esterification of CMF provides a unique range of ester products, whether by reaction of the carbonyl moiety of CMF or else by attack of the -Cl [50,80]. Production of 5-acetoxymethylfurfural, used as a biofuel additive, occurs through the application of alkylammonium acetate and acetonitrile (ACN) under mild conditions at room temperature and for only 10 min, Scheme 14 [50]. A 96% yield at 99% purity was reported after residue purification.



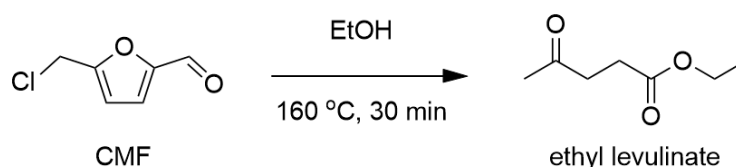
Scheme 14. Esterification of CMF to 5-acetoxymethylfurfural via alkylammonium acetate [50].

Dutta et al. described a system for the production of DMF as a final product through the intermediate production and isolation to two acetals, 2-(chloromethyl)-5-(diacetoxymethyl)furan and 2-(chloromethyl)-5-(dibutoxymethyl)furan [80]. Firstly, 2-(chloromethyl)-5-(diacetoxymethyl)furan was simply produced through the addition of acetic anhydride (Ac₂O) at 50 °C for 30 min at atmospheric pressure; this resulted in a yield of up to 92%, Scheme 15. A novelty of this production is the reported solvent-free reaction process using Ac₂O and an Amberlyst-15 acidic resin catalyst to perform the reaction.



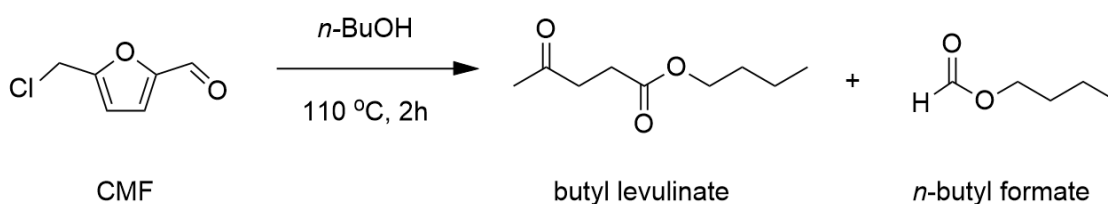
Scheme 15. Esterification of CMF to 2-(chloromethyl)-5-(diacetoxymethyl)furan under solvent-free conditions catalysed by the Amberlyst-15 acidic resin [80].

Finally, the production of ethyl levulinate has been reported through tandem rehydration of CMF followed by esterification of the levulinic acid intermediate. For this, the addition of alcohols, such as EtOH or *n*-BuOH, was required. Initially, the use of EtOH at 160 °C for 30 min produced ethyl levulinate with a yield of 85%, Scheme 16 [75].



Scheme 16. CMF to ethyl levulinate under ethanolic conditions [75].

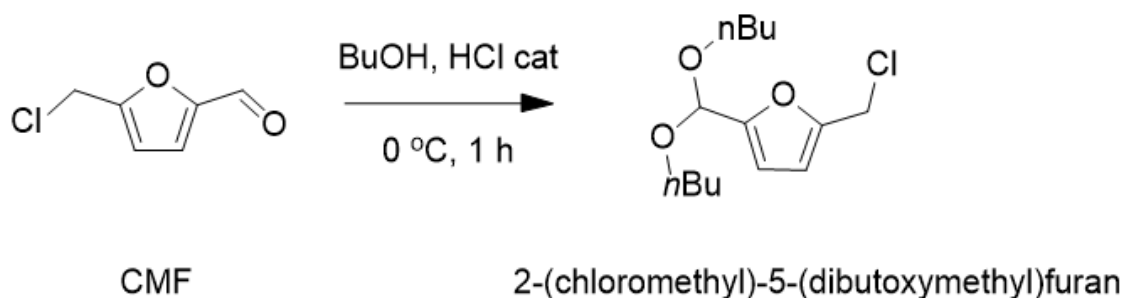
Furthermore, *n*-BuOH can be used to synthesise both butyl levulinate and *n*-butyl formate with a selectivity of 84% and 87%, respectively, at 110 °C for 2 h, Scheme 17. However, the *n*-butyl formate could not be isolated from the excess *n*-BuOH [75].



Scheme 17. Butyl levulinate and n-butyl formate from the addition of $n\text{-BuOH}$ [75].

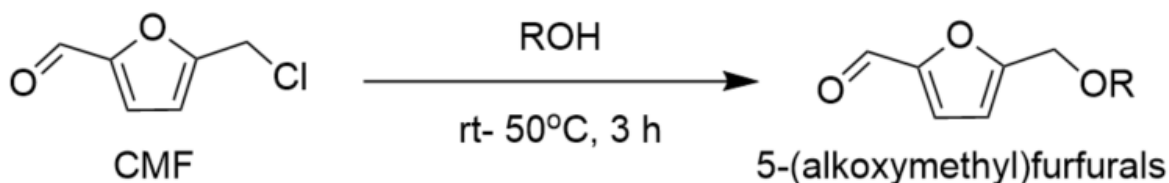
4.5. Etherification

Geminal etherification of CMF was reported, with a method of acetal production through the addition of $n\text{-BuOH}$ using HCl as homogeneous catalyst, which yielded 2-(chloromethyl)-5-(dibutoxymethyl)furan at 98%, as seen in Scheme 18. This process utilised a temperature of $0\text{ }^\circ\text{C}$ for an hour. The selection of $n\text{-BuOH}$ was guided by efforts to ensure the sustainability and greenness, relatively low cost, and low toxicity of said production process. Finally, the formation of a low-boiling-point azeotrope was determined to be favourable for subsequent separation and purification processes [80].



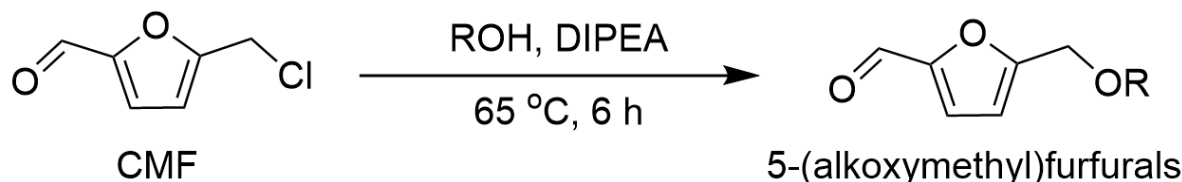
Scheme 18. Production of 2-(chloromethyl)-5-(dibutoxymethyl)furan from CMF [80].

Scheme 19 describes the preparation of a range of 5-(alkoxymethyl)furfurals, which are furan derivatives through the addition of alcohols [88]. Specifically, seven separate derivatives were described, four through the addition of alcohols as a solvent and three with the addition of a base, N,N -diisopropylethylamine (DIPEA). Firstly, the addition of methanol, ethanol, 1-propanol, and 1-butanol at $50\text{ }^\circ\text{C}$ for 3 h produced 5-(methoxymethyl)furfural, 5-ethoxymethylfurfural, 5-propoxymethylfurfural, and 5-butoxymethylfurfural, which were observed in yields of 91%, 90%, 92%, and 96%, respectively.



Scheme 19. Preparation of 5-(alkoxymethyl)furfurals from CMF, with ROH as a solvent where R = methyl to form 5-(methoxymethyl)furfural, or R = ethyl to form 5-ethoxymethylfurfural, or R = 1-propyl to form 5-propoxymethylfurfural, or R = 1-butyl to form 5-butoxymethylfurfural [88].

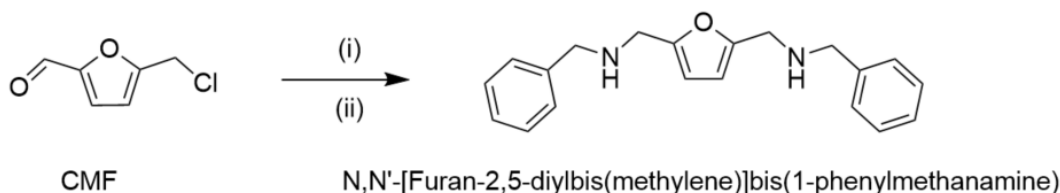
Next, the use of a base was investigated through the addition of DIPEA, as shown in Scheme 20. The trimethylamine (Et_3N) component of this base acted as a nucleophile and substituted the chloromethyl group in CMF and mildly inhibited the formation of humins whilst providing enhanced yields for secondary alcohols. The three 5-(alkoxymethyl)furfurals, 5-pentoxymethylfurfural, 5-hexoxymethylfurfural, and 5-(isopropoxymethyl)furfural were produced from 1-pentanol, 1-hexanol, and 2-propanol in yields of 93%, 94%, and 90%, respectively, at 65 °C for 6 h.



Scheme 20. Preparation of 5-(alkoxymethyl)furfurals from CMF, ROH in the ratio of 1.2 v/v%, where R = 1-pentyl to form 5-pentoxymethylfurfural, or R = 1-hexyl to form 5-hexoxymethylfurfural, or R = 2-propyl to form 5-(isopropoxymethyl)furfural [88].

4.6. Amination

Amination of CMF is frequently described in the literature, sometimes forming relatively complex molecules such as N,N' -[Furan-2,5-diylbis(methylene)]bis(1-phenylmethanamine) [46]. Scheme 21 describes the amination of CMF with benzylamine and Et_3N at room temperature for 16 h with a DCE extraction; subsequently, the solution was treated with $\text{NaBH}(\text{OAc})_3$ at room temperature for 16 h. This yielded N,N' -[Furan-2,5-diylbis(methylene)]bis(1-phenylmethanamine) in molar yields of 62%.

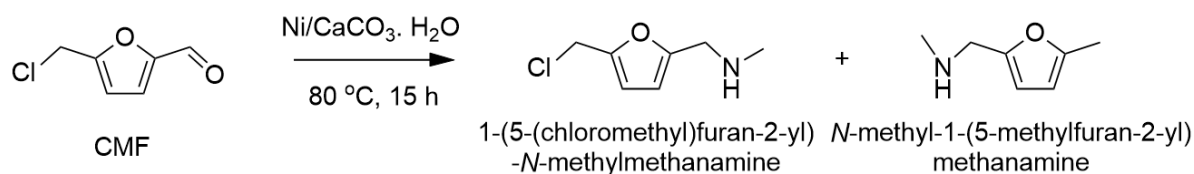


(i) Et_3N , benzylamine, DCE, rt, 16 h

(ii) $\text{NaBH}(\text{OAc})_3$, HOAc, rt, 16 h

Scheme 21. Amination of CMF with benzylamine [46].

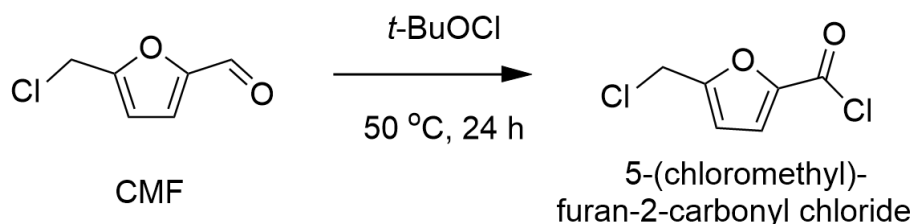
Jia et al. proposed a method of efficient reductive amination of CMF to secondary amines through the use of supercritical carbon dioxide with water as a hydrogen donor over Ni/CaCO_3 , as shown in Scheme 22 [89]. The two secondary amines produced, 1-(5-(chloromethyl)furan-2-yl)- N -methylmethanamine and N -methyl-1-(5-methylfuran-2-yl)- N -methylmethanamine, were both observed under identical conditions of 80 °C and 15 h with respective yields of 76% and 9%.



Scheme 22. Supercritical carbon dioxide-initiated amination of CMF [89].

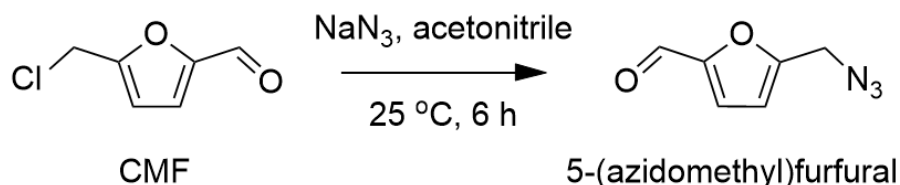
4.7. Other

The synthetic upgrading possibilities of CMF are vast and, as such, a varied array of reaction schemes and pathways are presented in the following section, highlighting the diversity of end-products possible. Dutta et al. reported the use of *t*-BuOCl to generate an acid chloride of CMF, 5-(Chloromethyl)furan-2-carbonyl chloride, as depicted in Scheme 23. This system at 50 °C for 24 h reported an in situ NMR-determined yield of 85%; however, the authors deemed isolation unnecessary as acid chlorides are generally only used as an intermediate for other carboxylic acid derivatives [87].



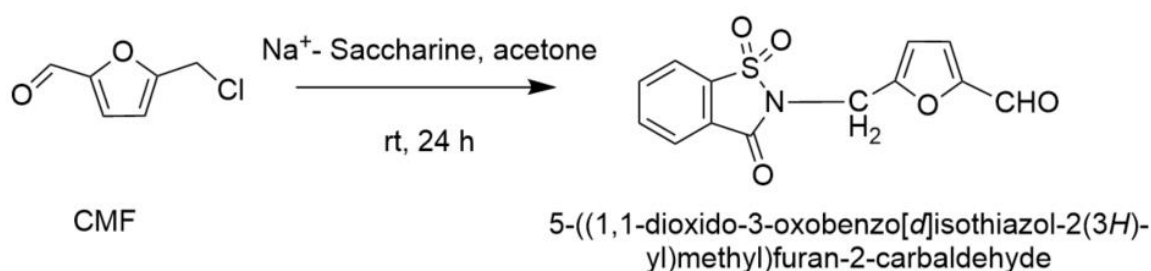
Scheme 23. *t*-BuOCl-driven reaction of CMF towards 5-(Chloromethyl)furan-2-carbonyl chloride [87].

The development of novel green platform chemicals is of continued importance; as such, the identification of a so-called “self-clicking” monomer in the form of 5-(azidomethyl)furfural would prove useful. This building block aimed to bridge the gap between renewable biomass and furfural-containing triazoles by providing a selective intermediate via the reactivity provided by the azide group [90]. This monomer was prepared from CMF under mild conditions of 30 °C for 6 h with the addition of acetone and sodium azide with a yield of 99% when isolated, as seen in Scheme 24.



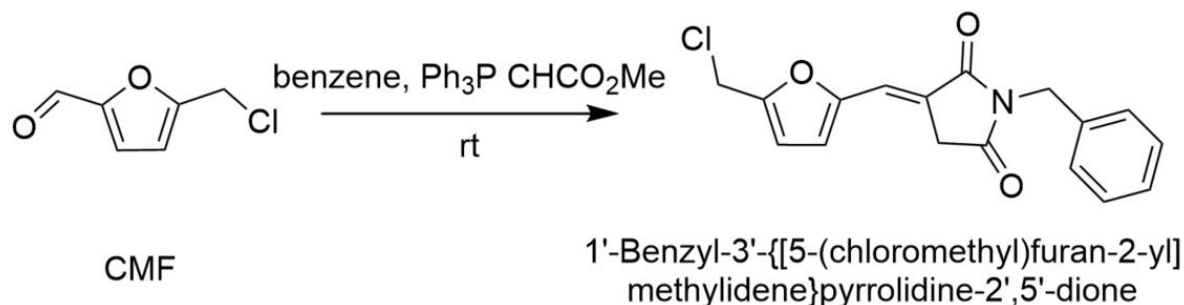
Scheme 24. Sodium azide-driven nucleophilic substitution of CMF towards a self-clicking monomer, 5-(azidomethyl)furfural [90].

With an eye on the synthesis of polymeric building blocks to be used in the synthesis of thermally stable polymeric Schiff bases, a CMF derivative based on the addition of saccharine was produced, as shown in Scheme 25. 5-((1,1-dioxido-3-oxobenzo[d]isothiazol-2(3*H*)-yl)methyl)furan-2-carbaldehyde was obtained via the addition of soluble saccharine in acetone at rt for 24 h [91]. This species was successfully isolated and identified in yields in excess of 95%. The authors detailed other derivatives such as a benzenesulphonic acid salt and thiourea, with yields of 95% and 96%, respectively.



Scheme 25. Saccharine-derived CMF derivative [91].

CMF has seen success over HMF in the production of enones through Wittig reactions of these furan components with the use of phosphoranes (Scheme 26). These so-called Wittig reactions generated a variety of enones with 1'-Benzyl-3'-([5-(chloromethyl)furan-2-yl] methylenemethylidene)pyrrolidine-2',5'-dione generated in a yield of 66% through the addition of benzene and phosphoranes at rt. These generated products were observed to hinder the presence of free radicals.



Scheme 26. CMF derivative obtained through a Wittig reaction with triphenyl pyrrolidone [92].

5. Conclusions and Outlook

Developments in the production process for furans over the recent century have continued with vigour. In addition to the wide expansion of technologies to produce HMF and furfural, in the last few years there has been increasing interest in the production of CMF. Despite the initial production of HMF and furfural in monophasic systems, these chemicals have seen the development of the use of biphasic systems to mitigate the formation of by-products, namely, LA, FA, and humins. CMF production has fully incorporated this approach for a reaction with in situ extraction, for which the higher hydrophobicity of this chemical shows more attractive partitioning in liquid–liquid media with respect to HMF. In addition, CMF has normally been produced at milder conditions than HMF, particularly temperature, where many of the works report catalysis below 100 °C as opposed to around 150 °C normally in the case of HMF.

With an eye on Green Chemistry, it is clear that the sustainable sourcing of CMF is an advantage, with different types of complex biomass being reported in addition to simple sugars. However, the biphasic systems used mostly include the use of aqueous biphasic systems based on halogenated solvents as extracting phases, with a prevalence of DCE. One key aspect to consider in the progress of CMF production is the substitution of such solvents for greener alternatives. To achieve this, an approach based on predicting the partitioning capabilities of solvents combined with consideration of the EHS aspects of solvents could be followed. For the former aspect, computational predictions can be made with tools like HSP or the COSMO-RS methods, whereas for the latter solvent profiling with guides like CHEM21 should be considered. Another aspect to consider is the lack of

information to evaluate eventual process scalability. For example, to date, only three studies have been published with kinetic models for CMF production, which is an essential element for reactor design and eventual process design, simulation, and techno-economic analysis. This techno-economic analysis could be guided by one of the three works detailing kinetics through practical implementation in ASPEN Plus. Additionally, an LCA for the production of HMF and FDCA could serve as a framework towards one applied to CMF.

Finally, another advantageous aspect of CMF is the rich synthetic possibilities that the –Cl moiety confers owing to this being an outstanding leaving group. As such, a wide array of chemicals can be produced through reactions of rehydration, hydrogenation, oxidation, esterification, etherification, and amination, among others, with applications as biofuels, materials like bioplastics, or ingredients in the formulation of different products. Future development of more complex routes from CMF as a building block will surely continue in the next years.

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Conflicts of Interest: The authors declare no conflict of interest.

Nomenclature

| | |
|-------------------|--|
| 4CA | Tetrachloroethane |
| 5MF | 5-methylfurfural |
| ACN | Acetonitrile |
| CMF | 5-chloromethylfurfural |
| CNT | Carbon nanotube |
| COSMO-RS | COnductor-like Screening MOdel for Real Solvents |
| DCE | 1,2-dichloroethane |
| DCM | Dichloromethane |
| DES | Deep eutectic solvents |
| DIPEA | <i>N,N</i> -diisopropylethylamine |
| DMF | 2,5-dimethylfuran |
| DMSO | Dimethyl sulfoxide |
| EHS | Environmental, health and safety |
| Et ₃ N | Triethylamine |
| FA | Formic acid |
| FDCA | 2,5-furandicarboxylic acid |
| GVL | γ -valerolactone |
| HBA | Hydrogen bond acceptor |
| HBD | Hydrogen bond donor |
| HMF | 5-hydroxymethylfurfural |
| HSP | Hansen solubility parameters |
| IL | Ionic liquid |
| LA | Levulinic acid |
| MIBK | Methyl isobutyl ketone |
| PCE | Perchloroethylene |
| PET | Polyethylene terephthalate |
| TCE | 1,1,2-trichloroethane |

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