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Diversification of the Renewable Furanic Platform via 5-(Chloromethyl)furfural-Based Carbon Nucleophiles

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KEYWORDS: biobased products; 5-(chloromethyl)furfural; Darzens reaction; platform molecules; Reformatsky reaction

Abstract

Biobased 5-(chloromethyl)furoate and 5-methylfuroate esters can be deprotonated to function as furylogous lithium enolates, and the former can also undergo zinc insertion to access Reformatsky-type chemistry. Carbon nucleophilicity represents hitherto little-explored reactivity in these key carbohydrate-derived platform molecules, expanding their synthetic utility and potentially opening up new sustainable product markets, *e.g.* in epoxy resins or biobased dyes.

Introduction

Much continues to be made of the potential of 5-(hydroxymethyl)furfural (HMF) **1** to serve as a carbohydrate-derived platform molecule for the production of biobased chemicals, despite the fact that it is only practically derivable from the food sugar fructose.[1] 5-(Chloromethyl)furfural (CMF) **2**, on the other hand, has attracted comparatively less attention, and yet can be made in high yield directly from raw biomass.[2] Both HMF **1** and CMF **2** have been used in a variety of synthetic contexts,[3,4] which can be summarized as shown in Figure 1.

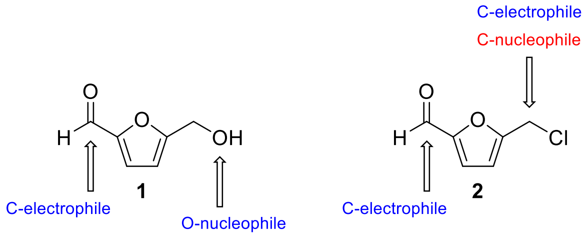

Figure 1. Charge affinities present in HMF (left) and CMF (right). Blue = native; red = this work.

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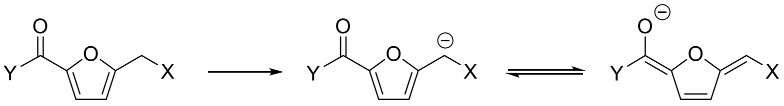
Since synthesis formally involves the generation of C–C bonds, the presence of a leaving group in CMF has always been a significant advantage over HMF, allowing the introduction of carbon nucleophiles by substitution,[5,6] as well as catalytic transition metal-mediated reactions.[7] In this work, we demonstrate even greater versatility by rendering the methylene group C-nucleophilic via the generation of either a furylogous enolate or an organometallic function.

Previous efforts to manipulate the chloromethyl group in CMF for synthetic purposes include conversion to a phosphonium salt[8] or sulfone,[9] which enables the generation of stabilized anions. Derivatives of this kind, however, have limited applications and show poor atom economy. Mikochik and Cahana described attack at the carbonyl group of **2** with an N-heterocyclic carbene, which expels the chlorine and formally imparts nucleophilic character to the methylene carbon, although in this case only towards protonation.[10] Most recently, Dai and coworkers adapted this same reactivity to carbon electrophiles, although the poor nucleophilicity restricted the scope to trifluoromethyl aryl ketones, oxalates, and related systems.[11]

In principle, CMF and its derivatives should be able to form furylogous enolates as depicted in Scheme 1, due to the relatively weak aromaticity of the furan ring. This effect should also help stabilize organometallic centers, where charge is concentrated on carbon. Attempting this with CMF itself would be challenging due to the reactivity of the aldehyde, and in fact the approach has been used to prepare a CMF homopolymer.[12] The corresponding esters, however, should possess sufficient stability to allow the kind of species represented in Scheme 1 to be realized. Recently, we showed how CMF could be converted in a single step to 5-(chloromethyl)furan-2-carbonyl chloride (CMFCC) **3**, which is readily quenched by alcohols to give 5-(chloromethyl)furoic acid esters.[13] We describe here the generation of carbon nucleophiles based around this system, thereby significantly enhancing the synthetic utility of the biobased furanic platform.



Scheme 1. Concept of furylogous enolate generation from CMF derivatives (X = H, Cl; Y = H, OR).

Results and Discussion

The direct oxidation of CMF **2** to CMFCC **3** is remarkably facile. t-BuOCl is made by mixing household bleach, t-butanol, and acetic acid, followed by phase separation. CMF is added and the resulting CMFCC

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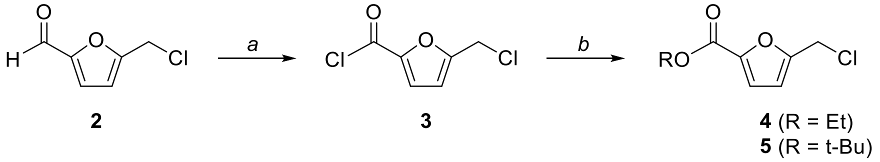
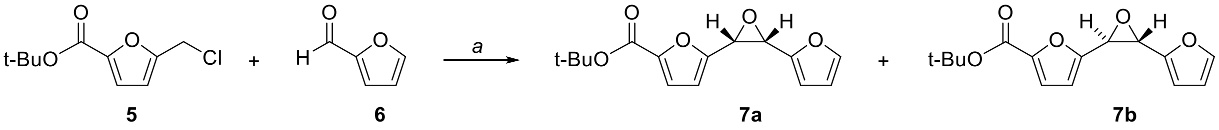
can be used directly without purification to make the 5-(chloromethyl)furoate esters like **4** and **5** (Scheme 2). Interestingly, although the chlorine in CMF **2** is quickly substituted by ethanol at room temperature,[14] it is preserved during the synthesis of the ester **4**, and can only be likewise displaced by heating at >100 °C.[13]



Scheme 2. Reagents and conditions: *a*. t-BuOCl, RT, 24 h, 80%; *b*. **4**: EtOH, 50 °C, 6h, 82%. **5**: t-BuOH, DMAP, 30 °C, 18 h, 70%.

Attempts to form an enolate directly from these esters using LDA in the presence of an aldehyde led to a Darzens type reaction to give epoxides. Yields were highest using the t-butyl ester **5**. Quenching with furfural **6** gave a mixture of stereoisomeric products **7a** and **7b** (Scheme 3). The reaction also works well with benzaldehyde (see SI).



Scheme 3. Reagents and conditions: *a*. 1.2 eq. LDA, THF, -78 °C to RT, 1 h, 63%, *cis*/*trans* ratio 60:40.

Success with the Darzens reaction led us to consider whether simple 5-methylfuroate esters would similarly deprotonate. These can be prepared in a single step from CMF.[10] Alternatively, we can apply the t-BuOCl + alcohol quench method to 5-methylfurfural (5-MF) **8** as shown in Scheme 4. We have previously described the preparation of 5-MF by reduction of CMF in >90% yield.[15] Deprotonation of **9** with LDA and quenching with furfural installed a 2-(furan-2-yl)-2-hydroxyethyl group (**10**), while homologation with methyl iodide gave 5-ethylfuroate ester **11**.

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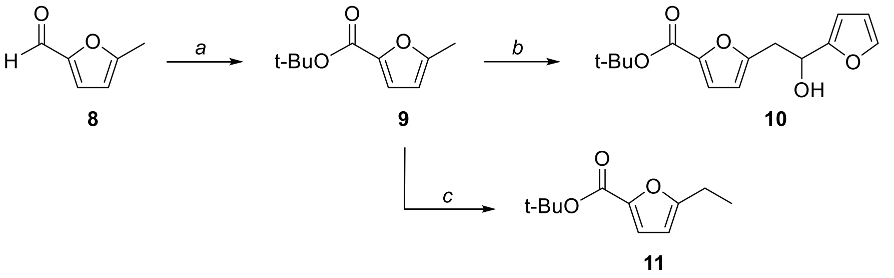

Scheme 4. Reagents and conditions: *a*. t-BuOCl, RT, 24 h, then t-BuOH, DMAP, 30 °C, 18 h, 62%; *b*. 1.2 eq. LDA, furfural, THF, -78 °C to RT, 12 h, 65%; *c*. 1.2 eq. LDA, MeI, THF, -78 °C to RT, 12 h, 63%.

Although direct deprotonation was facile for ester **9**, we also considered whether a CMF derivative could serve as a furylogous Reformatsky nucleophile. Zinc enolates are known for their gentle reactivity and functional group tolerance, such that the reaction could be attempted on the ethyl ester **4**. Interestingly, the literature already described the preparation of a zinc insertion product of **4**.[16] The authors reported attempts to use the resulting organozinc reagent for synthetic purposes, *i.e.* C-C bond formation using copper- and nickel-catalyzed coupling reactions, with limited success. We treated **4** with activated zinc in the presence of furfural **6** or 5-methylfurfural **8** to respectively produce **12**, the ethyl ester analogue of **10**, and **13**, in high yields (Scheme 5). The corresponding reaction with benzaldehyde gave the addition product in 99% yield (see SI).

Finally, given our strong interest in the production of sustainable dyes,[17] the opportunity to create extended conjugation was clearly present in **12** and **13**. That said, we tested acid-catalyzed dehydration on **12** and found it to be surprisingly sluggish. In terms of color performance, yellow product **14** was comparable in wavelength (λ_{max} 343 nm) and molar absorptivity (3.6×10^4 $M^{-1}cm^{-1}$) to the natural pigment retinoic acid.[18] Other green dehydration methods for **12** and **13** are currently under investigation. We also note the potential to exchange 2,5-diformylfuran[13] for **6**/**8** in the reaction in Scheme 5, which would ultimately deliver the even stronger chromophore **15**. Interestingly, the dehydration reaction to produce **14** also gave a significant amount of dimeric self-alkylation product **16** (24%). Materials like this may also be of potential interest as extended chromophores, assuming the unsaturation can be reintroduced to give **17**, which is a furan-substituted version of **15**. We have modeled the electronic absorption spectra of **15** and **17**, which are predicted to have maxima at 414 and 416 nm, respectively, centering their absorbance in the visible (violet) region of the spectrum (see SI).

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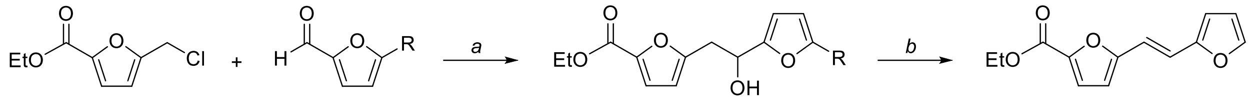
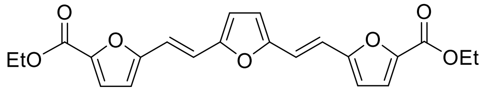


4 **6** (R=H) **8** (R=CH_3) **12** (R=H) **13** (R=CH_3) **14** (major isomer)

Scheme 5. Reagents and conditions: *a*. a. Zn, cat. I_2, THF, 40 °C, 18 h, 88% (**12**), 78% (**13**); *b*. Amberlyst 15, 3 Å molecular sieves, toluene, 60 °C, 7 h, 64%, *cis/trans* ratio 6:94.



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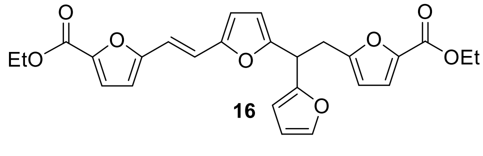

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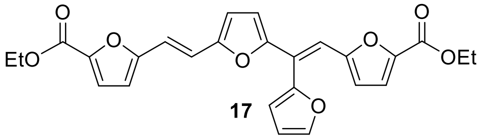

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Conclusion

Diversification of the synthetic utility of platform chemicals is the key to unlocking new markets for sustainable products. Up to now, the methylene group of CMF (and HMF) has seen limited engagement as a nucleophile. Here, we report the direct deprotonation of ester derivatives of CMF and 5-methylfurfural to give furylogous enolates. In the case of the chloromethylfuroate ester, the Darzens products represent a potentially new approach to preparing precursors to novel biobased epoxy resins. The deprotonated 5-MF ester reacts like any other enolate, giving typical addition and substitution products. Finally, chloromethylfuroates can also participate in Reformatsky-type reactivity, giving carbonyl addition products in high yields, the dehydration of which has the potential to expand the repertory of sustainable, biobased dyes.

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Supporting Information available: General experimental information, synthetic procedures and data, NMR spectra, UV-visible spectra, computational details

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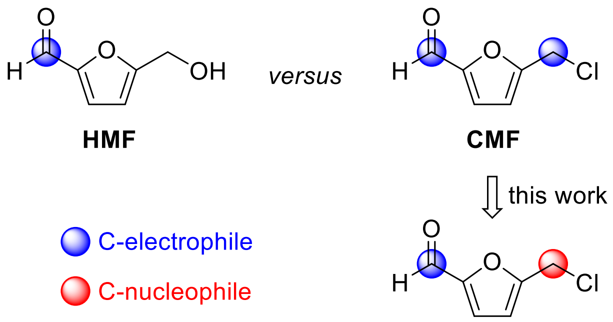
Graphical abstract:



Umpolung!: Native charge affinity patterns (electrophilic C in blue and nucleophilic C in red) are shown for **HMF** and **CMF**. The synthetic versatility of biomass-derived **CMF** is further expanded in this work by rendering the methylene carbon nucleophilic, either by deprotonation or metal insertion.

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