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Production of 5-(chloromethyl)furan-2-carbonyl chloride and furan-2,5-dicarbonyl chloride from biomass-derived 5-(chloromethyl)furfural (CMF)†

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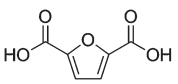
Acid chloride derivatives of 5-(chloromethyl)furan-2-carboxylic acid and furan-2,5-dicarboxylic acid (FDCA) can be produced in high yield by treatment of the precursor aldehydes 5-(chloromethyl) furfural (CMF) and 2,5-diformylfuran (DFF) with *tert*-butyl hypochlorite, which is inexpensively prepared from commercial bleach and *tert*-butanol. 5-(Chloromethyl)furan-2-carbonyl chloride (CMFCC) and furan-2,5-dicarbonyl chloride (FDCC) are highly useful intermediates for the production of furoate ester biofuels and polymers of FDCA.

Introduction

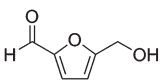
Few renewable polymers have made as forceful an impact on the landscape of petroleum alternatives as polyethylene furanoate (PEF). Serving both as a novel replacement for the high-volume polymer polyethylene terephthalate (PET) and a good alternative to bio-based PET, PEF is poised to make strong inroads into the PET market, due mainly to its outstanding performance (gas-barrier and mechanical properties), recyclability, and biodegradability.[1] Much of the present interest in PEF has been fueled by advances in the availability of the furan-2,5-dicarboxylic acid (FDCA) monomer **1**. Currently, the most efficient routes to FDCA are exclusively based on the oxidation of 5-(hydroxymethyl)furfural (HMF) **2**.[2] Uncertainties however regarding the economics of HMF production on a commercial scale have been a source of continuing speculation as to whether it can live up to its promise as a renewable platform molecule.[3] Difficulties specifically with its production from any feedstock other than fructose, and its isolation from the media in which it is produced, have no industrially practical resolutions to date.

Furans presenting a single carboxylic acid function have also been singled out as precursors to high-performance furoate ester biofuels,[4] polymers,[5] and fragments of cytokine interleukin-2 inhibitors[6] and anti-leukemia agents.[7] Substituted furoic acids are, in general, also approached synthetically *via* HMF by selective oxidation of the aldehyde group.[8]

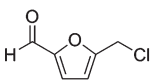
5-(Chloromethyl)furfural (CMF) **3** has been advanced as a functionally equivalent alternative to HMF that can be produced in high yield directly from raw biomass and, due to its hydrophobic character, presents no problems in its isolation.[9] Below, we demonstrate that CMF can be oxidized simply and directly to its corresponding acid chloride 5-(chloromethyl)-furan-2-carbonyl chloride (CMFCC) and that CMF-derived 2,5-diformylfuran (DFF) can likewise be oxidized to the diacid chloride furan-2,5-dicarbonyl chloride (FDCC), both of which are highly versatile synthetic intermediates for a range of green chemical derivatives.



FDCA 1



HMF 2



CMF 3

Results and discussion

The direct conversion of aldehydes to acid chlorides can be conveniently achieved using *tert*-butyl hypochlorite (*t*-BuOCl).[10] Although not frequently used in synthesis, the transformation is remarkably simple, involving the solvent-free reaction between the reagent and the aldehyde by stirring at room temperature. *tert*-Butyl hypochlorite can be produced in high yield in the course of a few minutes by mixing household bleach, acetic acid, and *tert*-butanol.[11] The reagent is isolated in a pure state by simply separating phases. In effect, the *tert*-butanol becomes a carrier of the bleach and enables it to work in a hydrophobic environment.

The reaction between CMF and *t*-BuOCl to give CMFCC **4** is shown in Scheme 1. Quantitative analysis by NMR using an internal standard indicated a CMFCC yield of 85%. Although **4** can be isolated, in practice, there is no real advantage in doing this, since acid chlorides are only ever intermediates en route

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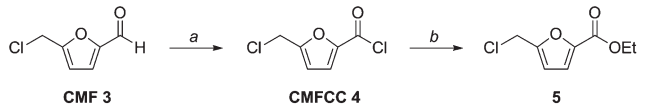


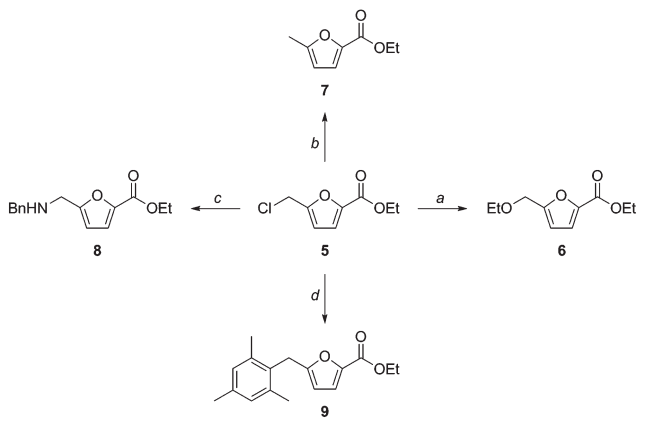
Scheme 1 Reagents and conditions: (a) *t*-BuOCl, 24 h; (b) EtOH, 50 °C, 6 h, 82% over 2 steps.

other carboxylic acid derivatives. Thus, for the purposes of demonstration, we quenched the product into ethanol to give the ethyl ester **5** and report the isolated yield over both steps which, in this case, is 82%.

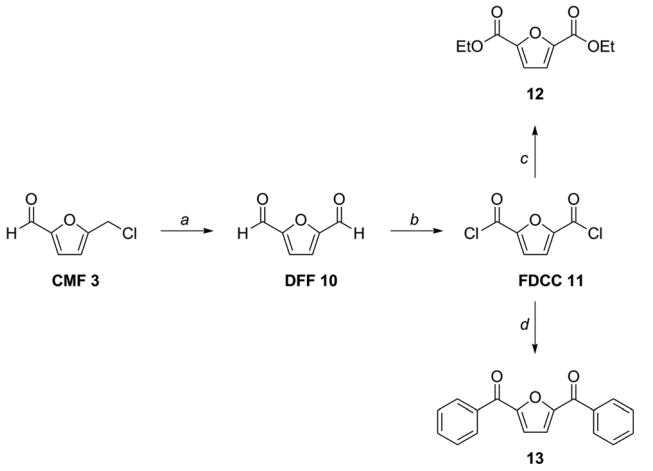
One thing that immediately stood out was the enhanced stability of the chloromethyl group in **5** compared to that of CMF **3**. Whereas dissolution of CMF in ethanol leads to 5-(ethoxymethyl)furfural,[9a] no analogous substitution was observed in CMFCC **4**, even after heating at 50 °C over the course of several hours. The substitution could however be forced by heating **5** in a closed vessel at 150 °C for 7 h (Scheme 2). The product **6** is a previously unreported molecule among a class of 5-(alkoxymethyl)furan-2-carboxylate esters that are little known in the chemical literature. The high stability of **6** compared to 5-(ethoxymethyl)furfural, itself a proposed biofuel,[12] suggests the potential of a similar application for **6** and its congeners.

We have also derivatized ester **5** by hydrogenolysis of the C–Cl bond to give ethyl 5-methylfuroate **7**. This and related "408"[13] esters are currently being commercialized as novel motor fuel oxygenates. In addition to being hydrophobic, high energy, non-toxic liquids, they also reduce particulate emissions, enhance lubricity, and improve cold-flow properties when blended with biodiesel. Substitution on the other hand with the nitrogen and carbon nucleophiles benzylamine and mesitylene leads respectively to derivatives **8** and **9** in high yields.

An obvious extension of the oxidation of CMF to CMFCC would be the analogous oxidation of 2,5-diformyl furan (DFF)



Scheme 2 Reagents and conditions: (a) EtOH, 150 °C, 7 h, 96%; (b) H_2, Pd/C, 2.5 h, 86%; (c) $BnNH_2$, 50 °C, 24 h, 82%; (d) 1,3,5-Me_3Ph, $AlCl_3$, 24 h, 95%.



Scheme 3 Reagents and conditions: (a) DMSO, 150 °C, 18 h, 81%;[14] (b) *t*-BuOCl, 24 h; (c) EtOH, 50 °C, 6 h; 76% over 2 steps; (d) PhH, $AlCl_3$, 20 h, 66% over 2 steps.

10 to access the bis(acid chloride) of FDCA, namely furan-2,5-dicarbonyl chloride (FDCC) **11**. Conveniently, Laugel and coworkers have reported the preparation of DFF by the simple heating of CMF in DMSO (Kornblum oxidation), providing **10** in >80% yield.[14] Treatment of DFF with *t*-BuOCl at room temperature cleanly provided FDCC **11** (Scheme 3), as demonstrated by ^{1}H NMR of the reaction mixture, which indicated a yield of 80% based on peak integration against an internal standard. As was the case for CMFCC **4**, we did not however isolate the FDCC but quenched it into ethanol, determining a yield of 76% of the corresponding diethyl ester **12** over the two steps. A particular advantage of FDCC **11** is that it is freely soluble in common organic solvents, compared to FDCA **1** which is soluble only in polar aprotic solvents such as DMSO. FDCC has been used as a starting material to make PEF and other poly(2,5-furandicarboxylates) based on a variety of diols,[15] so we do not repeat that chemistry here. Derivatization however by Friedel–Crafts acylation of benzene with **11** provided the bis(aryl) ketone **13**.

Conclusions

The synthetically versatile acid chlorides CMFCC **4** and FDCC **11** are two and three simple, efficient steps removed from raw biomass, respectively, being derived from the HMF-equivalent platform chemical CMF **3**. Although furan-2-carboxylates and furan-2,5-dicarboxylates have been produced from HMF, the process is burdened by the poor accessibility of HMF from biomass. The opportunity to access these acids, which are platform chemicals in their own right, in the form of soluble, conveniently derivatizable acid chlorides, will serve to broaden the scope of commercially relevant biorefinery products that can be derived from carbohydrates.

Experimental section

5-(Chloromethyl)furan-2-carbonyl chloride (CMFCC) 4 and ethyl 5-(chloromethyl)furan-2-carboxylate 5

5-(Chloromethyl)furfural **3** (2.226 g, 15.40 mmol) and *tert*-butyl hypochlorite (10.5 mL, 10.1 g, 92.7 mmol) were introduced into a 50 mL round-bottomed flask wrapped with aluminum foil. The mixture was stirred rapidly at room temperature under air. After 24 h, a measured amount of 1,4-dioxane was added as an internal standard and the yield of CMFCC **4** was determined to be 85% by ^{1}H NMR peak integration. The volatiles were evaporated at room temperature and the crude CMFCC **4** (2.90 g) was dissolved in anhydrous ethanol (20 mL). The clear yellow solution was stirred at 50 °C for 6 h. The solvent was evaporated and the residue was chromatographed using CH_2Cl_2/hexane (1 : 1 to 3 : 1 gradient) to give ethyl 5-(chloromethyl)furan-2-carboxylate **5** as a colorless oil (2.390 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, J = 3.5 Hz, 1H), 6.44 (d, J = 3.5 Hz, 1H), 4.55 (s, 2H), 4.31 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.35, 153.96, 145.02, 118.54, 111.37, 61.10, 36.68, 14.26. Performing this reaction on a 5× scale (10.47 g of CMF **3**) yielded 10.96 g of **5** (80.2%).

Furan-2,5-dicarbonyl chloride (FDCC) 11 and diethyl furan-2,5-dicarboxylate 12

2,5-Diformylfuran **10** (1.315 g, 10.60 mmol) and *tert*-butyl hypochlorite (14.4 mL, 13.8 g, 127 mmol) were introduced into a 50 mL round-bottomed flask wrapped with aluminum foil. The suspension was stirred rapidly at room temperature under air for 24 h, resulting in a clear yellow solution. A measured amount of 1,4-dioxane was added as an internal standard and the yield of FDCC **11** was determined to be 80% by ^{1}H NMR peak integration. The volatiles were evaporated at room temperature and the crude FDCC **11** (1.840 g) was dissolved in anhydrous ethanol (20 mL). The mixture was stirred at room temperature for 5 h. The solvent was evaporated and the residue was chromatographed using CH_2Cl_2/hexane (1 : 1 to 1 : 0 gradient) to give diethyl furan-2,5-dicarboxylate **12** as a yellow oil (1.700 g, 76%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 (s, 2H), 4.39 (q, J = 7.1 Hz, 4H), 1.38 (t, J = 7.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.06, 146.89, 118.22, 61.58, 14.24.

Experimental details of preparation of derivatives **6–9** and **13** are given in the ESI.†

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