

Sustainable Chemistry

High-Yielding Synthesis of 5-(alkoxymethyl)furfurals from Biomass-Derived 5-(halomethyl)furfural (X = Cl, Br)

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A series of 5-(alkoxymethyl)furfurals (AMFs) have been synthesized in excellent isolated yields (> 90%) by reacting biomass-derived 5-(chloromethyl)furfural (CMF) or 5-(bromomethyl)furfural (BMF) with monohydric alkyl alcohols (methanol to 1-butanol) at slightly elevated temperatures (RT–50 °C) and short reaction time (3 h). The modified work-up procedure minimizes side reactions while simplifying the isolation and purification of AMFs. Although higher primary alcohols like 1-pentanol and 1-hexanol and secondary alcohol like 2-propanol were found to be less reactive, use of *N,N*-diisopropylethylamine (DIPEA) as a base additive afforded AMFs in excellent yields within 6 h at 65 °C using only slight excess of the alcohol (1.2 eq.) reagent.

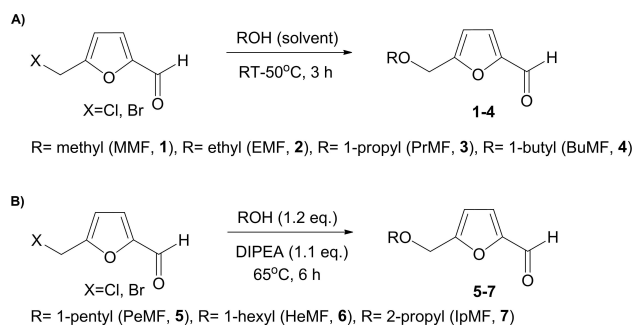
Introduction

Depleting resources, market volatility, and growing environmental concerns over the use of fossilized fuels have initiated a coordinated effort to find a renewable and sustainable source of carbon.^[1] Cellulosic biomass and waste products have been considered by many as a commercially-viable source of renewable fuels and chemical feedstock.^[2] 5-(Alkoxymethyl)furfural (AMF) is an interesting class of compound synthesized from the biomass-derived hexose sugars and carbohydrates with potential applications as liquid biofuels, chemical feedstock, and monomer for polymers.^[3–5] 5-(Ethoxymethyl)furfural (EMF) is overwhelmingly the most studied AMF. EMF is a potential biofuel candidate with an energy density 8.7 kW h L⁻¹ that is higher than ethanol (6.1 kW h L⁻¹) and comparable to gasoline (8.8 kW h L⁻¹) and diesel fuel (9.7 kW h L⁻¹).^[6] Synthesis of EMF has been attempted by acid-catalyzed ethanolysis of sugars like fructose and glucose, carbohydrates like starch and cellulose and also lignocellulosic biomass.^[7–9] The reaction is believed to proceed through the intermediary of 5-(hydroxymethyl)furfural (HMF). Although attractive as a one-pot synthesis of EMF, the yield and selectivity for the reactions are often poor.^[10] Besides, the relatively harsh reaction conditions lead to side reactions such as diethylether formation from ethanol and decomposition of HMF and EMF into humin. HMF has also been used as a

feedstock for the preparation of EMF.^[11] In a two-step strategy, HMF is first produced by acid-catalyzed dehydration of sugars and carbohydrates and then subjected to acid-catalyzed etherification reaction in ethanol. Although good yield and selectivity of EMF have been reported, the reaction generally requires high temperature and long reaction time and often ends up with a mixture of ethers and acetals.^[12] In addition, the commercial viability of this process ultimately depends on the efficient production of HMF from biomass which is still plagued with issues like efficient isolation and purification of HMF from the hydrophilic reaction media.^[13] Synthesis of AMFs has also been attempted from the congeners of HMF such as 5-(chloromethyl)furfural (CMF) and 5-(bromomethyl)furfural (BMF).^[14–15] CMF and BMF can be produced directly from sugars and lignocellulosic biomass.^[16–17] Being hydrophobic, unlike HMF, their isolation from the reaction media is relatively straightforward. CMF has been shown to participate in many derivative chemistries of HMF.^[18–20] Interestingly, alcohols can nucleophilically substitute the halogen atom in CMF and BMF, and unlike HMF the process does not require any acid catalyst. The reaction of alcohols with CMF and BMF produces one mole of HCl and HBr, respectively which can be recycled. Although high yields of EMF were reported using anhydrous ethanol, the formation of ethyl levulinate could not be avoided entirely during the work-up and purification process. Evolution of acid and the presence of trace water in alcohol triggers the ring opening of AMF into alkyl levulinates. In this regard, the use of an equivalent of base during the reaction has been found to minimize ring-opening product formation.^[21] However, the acid is converted into a salt; a process that introduces a waste stream and increases the cost of EMF as a biofuel. In this work, we have produced AMFs 1–7 (Scheme 1) in excellent isolated yields by reacting CMF and BMF with dry alcohols. The reactions were optimized on temperature, the ratio of reagents, and reaction time. In the case of AMF 1–4, the reactions completed within 3 h time at slightly elevated temperatures. A modified work-up procedure was adopted where the reaction mixture was first diluted in cold water and the product extracted in an organic solvent like chloroform. The process was found to minimize the ring-opening reaction significantly compared to the reported strategy of removing excess alcohol first by vacuum distillation. In general, alcohols with increasing alkyl chain were found to be less reactive in AMF formation. Therefore, in the case of AMFs 5–7, the reaction had to be performed using nearly an equivalent amount of *N,N*-diisopropylethylamine (DIPEA) as a non-nucleophilic organic base. We argued that these AMFs would likely be used for higher value

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Scheme 1. Preparation of AMFs from CMF and BMF using (A) alcohol as a solvent with no base additive and (B) slight excess of alcohol and an equivalent of DIPEA as a base.

applications and the cost of losing the acid as salt may be tolerated. Besides, the process allows using only slight excess high-boiling alcohols thereby simplifying the isolation and purification of AMFs. Excellent isolated yields of AMFs 5–7 were obtained under relatively mild reaction conditions (65 °C, 6 h).

Results and Discussion

Initially, synthesis of EMF, **2** was attempted using reported procedure where CMF was dissolved in excess anhydrous ethanol and mechanically stirred at room temperature till the conversion of CMF is complete.^[14] As reported, the reaction takes a long time (*ca.* 8 h) to complete. When the temperature was raised slightly to 45 °C, the reaction was found to complete within 3 h. No ring-opened product (*e.g.*, ethyl levulinate) formed under this condition as confirmed by FTIR and ¹H-NMR spectra of the crude reaction mixture. The reaction works similarly with BMF as the substrate. When CMF or BMF was reacted with methanol as solvent, the reaction completes within 3 h even at RT to yield 5-(methoxymethyl)furfural (MMF, **1**). The reaction was worked up following the same literature process where the excess alcohol was first removed by evaporation under vacuum.^[14] Interestingly, ethyl levulinate and some humin formed during the evaporation of alcohol as confirmed by spectroscopic analysis. This observation may be explained by the increasing concentration of dissolved HCl or HBr acid in ethanol during its evaporation that triggers the ring-opening reaction. Therefore, to avoid building-up acid concentration during work-up, the crude reaction mixture was first diluted in ice-cold water and the product extracted in chloroform to minimize the ethyl levulinate or humin formation. Using the modified work-up procedure, EMF was obtained in 90% and 92% isolated yields starting from CMF and BMF, respectively (Table 1, Entry 2). The same workup procedure afforded MMF, **1** in 91% and 93% isolated yields starting from CMF and BMF, respectively (Table 1, Entry 1). The trend of lower reactivity of alcohols with higher alkyl chain is pronounced in the case of 5-(propoxymethyl)furfural (PrMF, **3**) and 5-(butoxymethyl)furfural (BuMF, **4**). The conversion of CMF or BMF was not complete even after overnight reaction at RT. The reaction of CMF or BMF with 1-propanol and 1-butanol require 50 °C to

Entry	Substrate	Reaction condition ^[a]	Product	Yield (%) ^[b]
1	CMF (BMF)	RT, 3 h	MMF, 1	91 (93)
2	CMF (BMF)	50 °C, 3 h	EMF, 2	90 (92)
3	CMF (BMF)	50 °C, 3 h	PrMF, 3	92 (94)
4	CMF (BMF)	50 °C, 3 h	BuMF, 4	96 (97)

[a] The reaction uses 0.5 g of the substrate and 10 mL of anhydrous alcohol.
[b] Isolated yields. The number in parenthesis is the yield from BMF.

complete within 3 h. Following the same work-up procedure, PrMF, **3** and BuMF, **4** were isolated in 92% and 96% isolated yields using CMF as substrate (Table 1, Entry 3&4). BMF provided slightly better yields of AMFs when compared to CMF under comparable reaction conditions. All the reactions were performed using suitable alcohol as the solvent. When less alcohol reagent (2-5 eq.) was used, the reaction slowed down significantly and did not complete even after 6 h at 50 °C. Forcing the reaction to completion at higher temperatures led to the formation of alkyl levulinates and humin.

The reaction between CMF (or BMF) and higher alkyl alcohols like 1-pentanol and 1-hexanol did not complete after 6 h even at 65 °C. In an attempt to make the reaction faster, when the reaction was conducted at 80 °C, a noticeable amount of alkyl levulinates and humin formation were observed. We envisioned that a base additive would steer the reaction into completion in reasonable time and under milder conditions by quenching the acid produced during the reaction. Both inorganic and organic bases were screened, and their effects on the yield of 5-(pentoxymethyl)furfural (PeMF, **5**) are listed in Table 2. Initially, the reaction was performed

Entry	Substrate	Reaction condition ^[a]	Base	Yield (%) ^[b]
1	CMF	65 °C, 6 h	CaCO ₃	82 (6)
2	CMF	65 °C, 6 h	K ₂ CO ₃	86 (8)
3	CMF	65 °C, 6 h	DIPEA	94
4	CMF	65 °C, 6 h	Et ₃ N	60 ^[c]

[a] The reaction uses 0.5 g of CMF, 1.2 equivalent of 1-pentanol and 1.1 equivalent of base additive [b] Isolated yields of CMF, the number in the bracket is yield of pentyl levulinate. For entry 1&2, around 0.02 g of insoluble black solid was also recovered. [c] CMF reacted with Et₃N to form a substituted product.

using 1-pentanol a solvent as in the case of AMFs 1–4. However, removal of excess 1-pentanol is tedious and energy-intensive requiring longer time and stronger vacuum. To optimize the reaction further, when only slight excess (*i.e.*, 1.2 equivalent) of 1-pentanol was used, the reaction worked equally well and afforded PeMF, **5** in good yields. When CaCO₃ and K₂CO₃ were used as a base additive, PeMF, **5** was isolated in 82% and 86% yield, respectively (Table 2, Entry 1&2). Although the inorganic bases provided decent yields, the formation of pentyl levulinate and insoluble humin formation

could not be avoided altogether. This observation can be explained by the poor solubility of inorganic bases in 1-pentanol limiting their efficiency in quenching the acids liberated during reaction. Organic amines were then chosen as the base additive working under homogeneous reaction condition. When triethylamine was used as a base, significant side reaction was observed where triethylamine acted as a nucleophile and substituted the chloromethyl group in CMF (Table 2, Entry 4). *N,N*-Diisopropylethylamine (DIPEA) is a non-nucleophilic base frequently used in synthetic organic chemistry as a proton sponge. Use of an equivalent of DIPEA in the reaction medium virtually stopped the humin formation and ring-opening reaction altogether and provided PeMF, **5** in 94% isolated yield within 6 h at 65 °C.

Therefore, DIPEA was chosen as the base additive of choice for the synthesis of AMFs **5**–**7**. The reaction was also optimized on the equivalent of 1-pentanol used. The reaction works best with 1.2 equivalent of 1-pentanol with 93% isolated yield of **5** (Figure 1). Higher equivalents of 1-pentanol do not have a

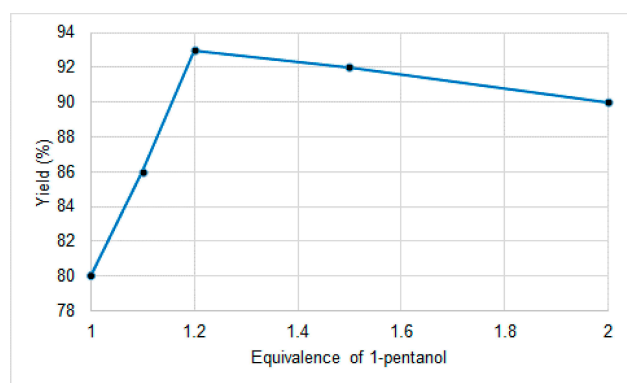


Figure 1. Effect of equivalence of 1-pentanol on the isolated yield of PeMF, **5**.

significant impact on the yield. However, lower equivalents of 1-pentanol drastically lowered the yield.

AMFs (**5**–**7**) were prepared from CMF, and BMF using the optimized conditions and their yields are tabulated in Table 3.

Entry	Substrate	Reaction condition ^[a]	Product	Yield (%) ^[b]
1	CMF (BMF)	65 °C, 6 h	PeMF, 5	93 (94)
2	CMF (BMF)	65 °C, 6 h	HeMF, 6	94 (96)
3	CMF (BMF)	65 °C, 6 h	IpMF, 7	90 (92)

[a] The reaction uses 0.5 g of the substrate and 1.2 equivalent of anhydrous alcohol in the presence of DIPEA (1.1 eq.). [b] Isolated yields. The number in parenthesis is the yield from BMF.

As observed in the case of AMFs **1**–**4**, BMF provided slightly better yields of AMF **5**–**7** compared to CMF. For example, PeMF, **5** and 5-(hexyloxymethyl)furfural (HeMF, **6**) were obtained in 93% and 94%, respectively starting from CMF. Use of BMF as

the substrate provided **5** and **6** in 94% and 96% isolated yields under identical reaction conditions (table 3, entry 1&2). When 2-propanol was used, 5-(isopropoxymethyl)furfural (IpMF, **7**) was synthesized in 90% and 92% isolated yields from CMF and BMF, respectively.

Conclusions

A series of 5-(alkoxymethyl)furfurals have been synthesized in excellent isolated yields starting from biomass-derived 5-(halomethyl)furfural (X=Cl, Br). The lower alcohols (methanol to 1-butanol) were used as a solvent for the nucleophilic substitution reaction that completes within 3 h at slightly elevated temperatures. A general synthetic protocol was developed that does not require any base additive. The reactivity of higher primary alcohols and secondary alcohol were found to be less, but DIPEA was found to be an efficient organic base additive that provided AMFs in excellent yields using only slight excess of the alcohol reagent.

Supporting Information

FTIR, ¹H-NMR, and ¹³C-NMR spectra of all synthesized compounds are available online as supporting information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: biofuel · biomass · ethoxymethylfurfural · renewable resources · sustainable chemistry

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