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# Etherification Reactions of Furfuryl Alcohol in the Presence of Orthoesters and Ketals: Application to the Synthesis Furfuryl Ether Bio-Fuels

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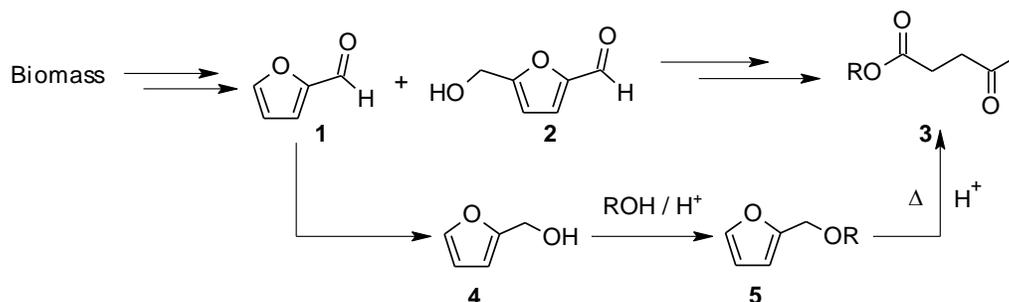
ABSTRACT: Strategies for the efficient transformation of abundant and sustainable bio-derived molecules, such as furfuryl alcohol (FAlc), into higher value products is currently a vibrant research area. Herein, we demonstrate that furfuryl ethers, which are of significant interest as bio-renewable fuel additives, are efficiently produced employing an etherification reaction of furfuryl alcohol and short chain alkyl alcohols in the presence of a recyclable ZSM-5 catalyst and an orthoester, such as trimethyl orthoformate (TMOF) or triethyl orthoformate (TEOF), used as a sacrificial reagent. These etherification reactions proceed at significantly low temperatures than previous etherification procedures, and provide the furfuryl ether products in high yield.

Importantly, the low temperature employed improves selectivity by minimizing the formation of hydrolysis products, and the competing polymerization reactions leading to humin by-products. By carrying out the reaction in higher alcohol solvents, such as ethanol, 1-propanol and 1-butanol, it is possible to capitalize on the ability of ZSM-5 to catalyze the orthoester exchange reaction of TMOF or TEOF to produce the corresponding furfuryl ethers in a novel, telescoped orthoester exchange-etherification reaction sequence. Finally, we also demonstrate that the etherification reaction proceeds efficiently in the presence of acetals and ketals, such as dimethoxy propane (DMOP) and diethoxypropane (DEOP). This latter development is highly significant given the greater scope for the regeneration of acetal and ketal reagents.

## INTRODUCTION

The increasing demand for fossil fuel resources, particularly for the transportation market, comes at a time of diminishing reserves of these non-renewable resources, and an increasing awareness of the influence of greenhouse gases on global climate change which has highlighted the need to develop fuels sources derived from sustainable and renewable carbon sources. These factors have led to considerable interest in alternative strategies for energy production which have reduced environmental impact, and which also support local agricultural economies. Biomass valorization, in particular, has attracted considerable interest as a sustainable and renewable source of both energy and feedstock chemicals for the chemical industry.<sup>1-3</sup> The valorization of inedible lignocellulose residues, sustainably sourced from agriculture and forestry activities, is attracting significant current interest as a low cost and abundant source of materials for the production of a range of chemical entities which can be subsequently converted into useful consumer products.<sup>4,5</sup> One of the best studied and commercially viable approaches to lignocellulosic-fractionating technologies developed to date involves the acid catalyzed hydrolysis of polysaccharides to their monomeric constituents, which are then in turn converted to furfural **1** and 5-hydroxymethyl furfural (HMF) **2** (Scheme 1).<sup>6</sup>

**Scheme 1. Conversion of Biomass to Furfural and 5-Hydroxymethyl furfural (HMF)**



While routes for the subsequent conversion of 5-hydroxymethyl furfural into levulinic acid and levulinate esters **3** and 2,5-dimethylfuran for use as biofuels are well established,<sup>7,8</sup> similar routes for the valorization of furfural as a platform for biofuel production are less well established, although this oversight is being rapidly addressed.<sup>9,10</sup> One important transformation is the hydrogenation of furfural to furfuryl alcohol (FAlc, **4**), and its subsequent conversion into furfuryl ethers, such as ethyl furfuryl ether (EFE, **5a** R = ethyl). These ether products are of considerable recent interest as they are intermediates in the acid catalyzed hydrolysis of FAlc to levulinate ester fuels,<sup>11-14</sup> and have also been identified as a potential bio-fuel components in their own right.<sup>9,15</sup> Recent work in this area has investigated the formation of furfuryl ethers by a dehydrative etherification reaction of FAlc with short chain alkyl alcohols, typically ethanol, in the presence of either sulfuric acid or heterogeneous zeolite catalysts at temperatures between 125–150 °C.<sup>9,15</sup> While this approach has proved to be effective for the synthesis of EFE, the overall process is inefficient, both in terms of the high energy consumption due to the high temperatures and extended reaction times employed, and the limited overall conversion to the desired ether product which is typically 30–50% even at high FAlc conversions.<sup>9</sup> The efficiency of this process is further limited by the conversion of FAlc to insoluble humin by-products which precludes the recycling of unreacted starting material, and also the hydrolysis of EFE under the high temperatures employed to ethyl levulinate, levulinic acid and lactone products.<sup>9,16</sup>

As part of our ongoing studies to develop novel reaction strategies,<sup>17,18</sup> we recently reported a facile protocol for the dehydrative etherification of alkyl alcohols, diols and triols with alcohols catalyzed by nanoporous aluminosilicate materials to give the corresponding ether products in high yield and with excellent selectivity.<sup>19,20</sup> In common with related strategies, the relatively high reaction temperatures required limits the scope of the reaction particularly in the case of thermally

unstable substrates or products, and we were motivated to seek alternative strategies that might be more applicable to these substrates, especially at extremes of pH, such as FAlc. With this in mind, we were intrigued by the work of Kumar *et al.*, who reported that orthoesters act as sacrificial reagents to promote the etherification reactions of alcohols under acid catalysis at room temperature.<sup>21</sup> While the use of a sacrificial reagent is inherently atom inefficient, the potential overall savings both in terms of energy and improved selectivity warranted further investigation. In addition, we reasoned that it might prove possible to overcome these limitations by employing reagents which can be regenerated under the reaction conditions. Herein we report our studies on the etherification of FAlc in the presence of orthoesters and alcohols employing a commercially available zeolite catalyst, the subsequent development of a novel telescoped protocol to access ethers derived from higher alcohols, and our initial studies on the etherification reactions of FAlc in the presence of acetals and ketals.

## **RESULTS AND DISCUSSION**

Our initial investigations employed the commercially available ZSM-5 zeolite (Si/Al ratio = 30:1, ZSM-5-(30)) catalyst in ethanol under relatively low catalyst loadings. This catalyst was chosen, in preference to our own nanoporous materials, as it has previously been reported as the most efficient catalyst to date for dehydrative etherification reactions of FAlc to EFE.<sup>9,15</sup> Our initial work concentrated on two factors identified as critical for efficient EFE production, these being the reaction temperature and the ratio of FAlc to ethanol. In addition to these factors, we also required the reaction to be rapid, and to be complete within short reaction times to minimize subsequent reaction of EFE under the reaction conditions.

We initially investigated etherification reactions at 40 °C in the absence of the orthoester to establish the extent of EFE formation. As reported, reducing the temperature from 125 °C to 40 °C significantly reduced the rate of reaction,<sup>9</sup> and conversions to EFE did not exceed 10%. Similarly, reactions containing FAlc and triethyl orthoformate (TEOF, **6a**) with no catalyst present provided no ether products, and starting material was recovered unchanged (Table 1, entries 1 and 2).

**Table 1: Optimization of the Etherification reaction of FAlc in alcohol solvents<sup>a</sup>**

OCC1=CC=C(O)C=C1  $\xrightarrow[\text{CH(OR)}_3 \text{ (1 equiv), ROH}]{\text{ZSM-5(30), 40}^\circ\text{C}}$  ORCC1=CC=C(O)C=C1  
**4**  **5a-b** R = Et, Me

Entry	Catalyst (mg)	Orthoester/ROH	FAlc:ROH Ratio (mmol)	Conversion (mol%) <sup>b</sup>	Yield <b>5</b> (mol%) <sup>c</sup>	Humins (mol%)	Mass Balance (mol%) <sup>d,e</sup>
1	20	EtOH	-	9	7	2	98
2	-	<b>6a</b> /EtOH	1:15	0	0	2	98
3	20	<b>6a</b> /EtOH	1:2	53	24	29	71
4	20	<b>6a</b> /EtOH	1:10	59	42	17	83
5	20	<b>6a</b> /EtOH	1:15	66	50	16	84
6	20	<b>6a</b> /EtOH	1:15	65	48 <sup>f</sup>	17	83
7	20	<b>6a</b>	-	77	33	44	56
8	40	<b>6a</b> /EtOH	1:15	63	48	15	85
9	40	<b>6a</b> /EtOH	1:15	92	73 <sup>g</sup>	19	81
10	10	<b>6a</b> /EtOH	1:15	55	33	22	78
11	20	MeOH	-	9	7	2	98
12	-	<b>6b</b> /MeOH	1:15	0	0	2	98
13	20	<b>6b</b> /MeOH	1:15	57	42	15	85
14	10	<b>6b</b> /MeOH	1:15	25	18	17	93

<sup>a</sup>Experimental conditions: The catalyst was added to a solution of furfuryl alcohol (1 mmol) and orthoester (1 mmol) in the specified solvent in a sealed reaction vessel and heated to 40 °C for 2 hours.

<sup>b</sup>Quantity of FAlc consumed as determined by quantitative <sup>1</sup>H NMR spectroscopy of the crude reaction mixture. <sup>c</sup>Determined by quantitative <sup>1</sup>H NMR spectroscopy and GC–MS analysis of the crude reaction mixture. <sup>d</sup>Sum of soluble materials identified by quantitative <sup>1</sup>H NMR spectroscopy and GC–MS analysis. <sup>e</sup>Reactions contained <5% ethyl levulinate, levulinic acid and angelica lactone by quantitative <sup>1</sup>H NMR spectroscopy of the crude reaction mixture. <sup>f</sup>Reaction using recycled catalyst.

<sup>g</sup>Additional 0.5 equiv TEOF added after 1 hr.

Gratifyingly, the addition of one equivalent of TEOF under relatively concentrated reaction conditions (FAlc/EtOH ratio = 1:2) led to moderate yields of EFE (entry 3) from moderate FAlc conversions (~50%) in short reaction times (2 hours). As previously observed,<sup>9</sup> carrying out the reaction under more dilute conditions led to significant improvements in yields of EFE, which now approached 50% with significantly reduced humin formation (entries 4 and 5). Importantly, the ZSM-5-(30) catalyst is fully recyclable, and displayed identical reactivity after isolation from the reaction mixture and recalcination (entry 6).<sup>22,23</sup> Interestingly, the etherification reaction also proceeded in the absence of any additional ethanol under solventless reaction conditions, albeit with reduced yield and significant humin formation (entry 7). Doubling the amount of catalyst had minimal effect on the overall production of EFE, although it was noted that there was complete consumption of TEOF (entry 8). We reasoned that TEOF is the limiting factor under these conditions, and were gratified to observe that the additional of an extra 0.5 equivalent of TEOF after one hour led to almost complete consumption of FAlc with excellent conversions to EFE (entry 9). A reduction in the amount of catalyst led to only moderate yields of EFE, albeit with a corresponding reduction in the consumption of FAlc (entry 10). Presumably, in this case, catalyst deactivation due to humin formation becomes the determining factor in EFE production, as significant quantities of unreacted TEOF remained.<sup>16,18</sup> The etherification reaction also proceeded efficiently in methanol in the presence of trimethyl orthoformate (TMOF, **6b**), to provide the corresponding methyl ether **5b** in broadly similar yields to reactions employing TEOF (entries 13–14). In all cases, formation of lactone or hydrolysis products was <5% as determined by quantitative <sup>1</sup>H NMR spectroscopy of the crude reaction mixtures. Furthermore, no mixed ethers products were observed, presumably due to the decreased reactivity of the unactivated alcohols and the low reaction temperatures employed.

We next undertook a short study to determine the effect of changing the FAlc/orthoester ratio. Decreasing the quantity of TEOF led to decreased EFE formation with a corresponding decrease in the consumption of FAlc. The complete consumption of TEOF in this case suggests that TEOF is the limiting factor (Table 2, entry 1). The addition of increased quantities of TEOF gave no additional improvement in yields of EFE (entry 3). These reactions contained significant quantities of unreacted TEOF which may indicate that catalyst deactivation is also the determining factor here. Presumably, this arises as a consequence of the facile generation of the furfuryl cation under the reaction conditions, and its subsequent conversion into humin by-products.<sup>16,24,25</sup> Indeed, the reaction of FAlc with TEOF in ethanol employing used catalyst which had not been recalcedined gave less than 10% yields of EFE.

**Table 2: The Effect of Orthoester Ratio**

Entry	Orthoester (equiv)	Solvent	Conversion (mol%) <sup>b</sup>	Yield 5 (mol%) <sup>c</sup>	Humins (mol%)	Mass Balance (mol%) <sup>d</sup>
1	<b>6a</b> (0.5)	EtOH	37	23	14	86
2	<b>6a</b> (1.0)	EtOH	57	44	13	87
3	<b>6a</b> (1.5)	EtOH	62	40	22	78

<sup>a</sup>Experimental conditions: The catalyst (20 mg) was added to a solution of furfuryl alcohol (1 mmol) in ethanol (1 mL) and TEOF in a sealed reaction vessel and heated to 40 °C for 1 hr. <sup>b</sup>Quantity of FAlc consumed as determined by quantitative <sup>1</sup>H NMR spectroscopy of the crude reaction mixture. <sup>c</sup>Determined by quantitative <sup>1</sup>H NMR spectroscopy and GC–MS analysis of the crude reaction mixture. <sup>d</sup>Sum of soluble materials identified by quantitative <sup>1</sup>H NMR spectroscopy and GC–MS analysis.

We next undertook a study of the etherification reaction in dimethyl carbonate (DMC), a solvent which has been proposed as an alternative environmentally benign replacement for more traditional solvents.<sup>26</sup> These reactions proceeded in the absence of an alcohol solvent, with the orthoester itself acting as a source of alcohol. As previously, reaction of FAlc with one equivalent of TMOF in the absence of catalyst provided no ether products (Table 3, entry 1). Low catalyst loadings (10 mg) provided only small quantities of the methyl furfuryl ether (MFE) (entries 2 and

3), while increased loadings (20 mg) provided good conversions to MFE (entry 4) which were not improved by changing the quantity of TMOF present (entries 5 and 6). In all of these cases, an additional orthoester product, tentatively identified by <sup>1</sup>H NMR and GC-MS data as being derived from mono exchange of TMOF with FAlc, was present, although it did not prove possible to isolate this compound (Figure S6). In addition, small quantities of the symmetrical dimeric ether product derived from FAlc were also observed. High catalyst loadings (50 mg) provided good conversions to MFE but with significant humin formation in addition to small quantities of methyl levulinate, which were typically ~5%, (entries 7 and 8).

**Table 3: Etherification Reactions of FAlc and TMOF in DMC<sup>a</sup>**

Entry	Catalyst (mg)	Time (h)	Orthoester (equiv)	Conversion (mol%) <sup>b</sup>	Yield 5 (mol%) <sup>b</sup>
1	-	2	<b>6b</b> (1.0)	0	0
2	10	2	<b>6b</b> (1.0)	44	13
3	10	2	<b>6b</b> (2.0)	64	16
4	20	2	<b>6b</b> (1.0)	65	30
5	20	2	<b>6b</b> (0.5)	41	16
6	20	2	<b>6b</b> (1.5)	68	28
7	50	1	<b>6b</b> (1.0)	97	58 <sup>c</sup>
8	50	2	<b>6b</b> (1.0)	95	60 <sup>c,d</sup>
9	10	2	<b>6b</b> (1.0)	70	21 <sup>e</sup>
10	20	2	<b>6b</b> (1.0)	77	39 <sup>e</sup>
11	50	1	<b>6b</b> (1.0)	98	48 <sup>c,e</sup>
12	50	2	<b>6b</b> (1.0)	98	55 <sup>c,d,e</sup>
13	10	2	<b>6a</b> (1.0)	66	20
14	20	2	<b>6a</b> (1.0)	77	36
15	50	2	<b>6a</b> (1.0)	85	52 <sup>c</sup>

<sup>a</sup>Experimental conditions: The catalyst was added to a solution of furfuryl alcohol (1 mmol) and orthoester (1 mmol) in DMC (1 mL) in a sealed reaction vessel and heated to 40 °C. <sup>b</sup>Quantity of FAlc consumed as determined by quantitative <sup>1</sup>H NMR spectroscopy of the crude reaction mixture. <sup>c</sup>Reaction contains ~5% levulinate ester by quantitative <sup>1</sup>H NMR spectroscopy of the crude reaction mixture. <sup>d</sup>Catalyst added in two 25 mg portion. <sup>e</sup>Reaction at 60 °C.

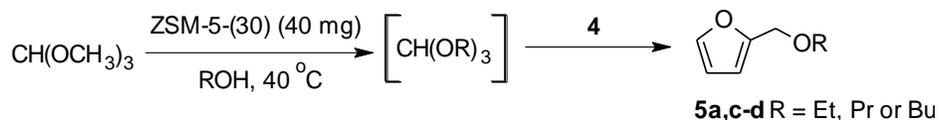
Increasing the reaction temperature to 60 °C had little overall effect on either MFE formation or FAlc conversion (entries 9–12). The reactions of FAlc with TEOF in DMC displayed a similar trend, with good conversions to EFE only achieved at higher catalyst loadings (entries 13–15). In line with previous literature reports<sup>20,27</sup>, none of the corresponding methyl ether MFE, formed by direct reaction of FAlc with DMC or by reaction with methanol formed by DMC composition, was detected in these reaction mixtures.

The observation that ZSM-5-(30) effectively catalyzes orthoester exchange reactions in the presence of alcohols led us to next consider the development of a novel orthoester exchange-etherification reaction sequence, in which the required orthoesters are produced from TMOF and the corresponding alcohol in situ without the requirement for prior synthesis and isolation. Telescoped reaction protocols, where multiple synthetic transformations are achieved without the isolation and purification of intermediates, have been the subject of significant recent interest as they offer improved efficiency due to the reduction in the number of synthetic steps. In addition, the elimination of work-up procedures and the subsequent reduction in the quantity of solvents employed leads to a significant overall improvement in atom efficiency.<sup>28-30</sup> Our own studies in this area have concentrated on telescoped procedures in which one catalyst is responsible for catalyzing two distinctly different synthetic transformations which are less common.<sup>31</sup>

Our initial investigations envisaged two potential strategies. A sequential reaction protocol in which the desired orthoester is synthesized from TMOF and an alcohol followed by the addition of FAlc, and a tandem reaction sequence in which all of the reagents are present at the beginning of the reaction. In the latter case, orthoester exchange occurs in the presence of an excess of alcohol solvent in order to minimize the competing formation of the methyl ether by-product. Our sequential reaction protocols were initially carried out at 60 °C in a reaction vessel open to the

atmosphere in order to remove methanol produced during the exchange reaction before cooling to 40 °C for the addition of FAlc. The tandem process was carried out as previously in a sealed reaction vessel at 40 °C. In both cases the catalyst loading was increased to 40 mg in order to minimize reaction times. We were gratified to observe that, in both cases, the sequential and tandem reactions proceeded rapidly to give good yields of furyl ether products derived from ethanol **5a**, 1-propanol **5c**, and 1-butanol **5d** with good to high selectivity for the higher ether products (Table 4). While most interest in furfuryl alcohol derived ether biofuels has centered on EFE, the physical properties of ethers **5c** and **5d** have been investigated for use as biofuels<sup>32</sup>.

**Table 4: Telescoped Orthoester Exchange-Etherification Reaction Protocols**

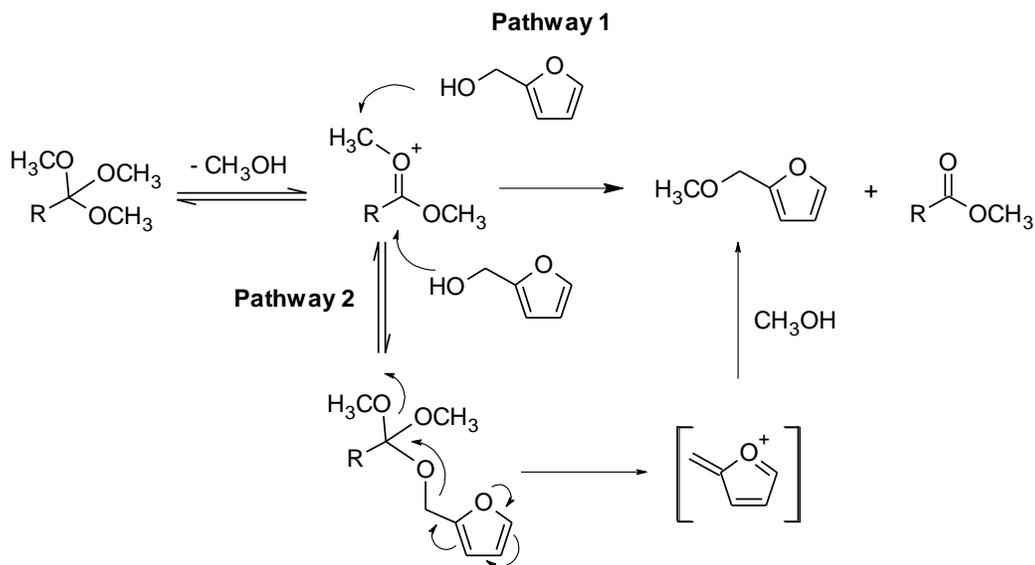


Entry	Orthoester	ROH	Selectivity (%) <sup>a</sup>	Conversion (mol%) <sup>b</sup>	Yield <b>5</b> (mol%) <sup>a</sup>	Humins (mol%)	Mass Balance (mol%) <sup>c</sup>
1	<b>6b</b>	EtOH	6:1	45	42 <sup>d</sup>	3	97
2	<b>6b</b>	PrOH	9:1	37	30 <sup>e</sup>	7	93
3	<b>6b</b>	PrOH	6:1	54	43 <sup>d</sup>	11	89
4	<b>6b</b>	BuOH	5:1	44	35 <sup>e</sup>	11	89
5	<b>6b</b>	BuOH	7:1	49	37 <sup>d</sup>	12	88

<sup>a</sup>Determined by quantitative <sup>1</sup>H NMR spectroscopy and GC–MS analysis of the crude reaction mixture. <sup>b</sup>Quantity of FAlc consumed as determined by quantitative <sup>1</sup>H NMR spectroscopy of the crude reaction mixture. <sup>c</sup>Sum of soluble materials identified by quantitative <sup>1</sup>H NMR spectroscopy and GC–MS analysis. <sup>d</sup>Tandem Reaction. <sup>e</sup>Sequential reaction.

The observation that orthoester exchange reactions are occurring under the reaction conditions also led us to reconsider the mechanism of the etherification reaction. Kumar et al originally proposed the formation of a cationic species, produced by partial hydrolysis of the orthoester, followed by transfer of an alkyl group to produce the unsymmetrical ether (**Scheme 2**, Pathway 1).<sup>21</sup>

## Scheme 2: Mechanism of the Orthoester Promoted Etherification Reaction



An alternative mechanism, in which the formation of a mixed orthoester leads to an intermediate susceptible to direct nucleophilic attack by alcohols (Scheme 2, Pathway 2), or more likely, promotes the formation of the furfuryl cation intermediate could also be proposed.<sup>33,34</sup> Similar activation strategies, in which alcohol substrates are converted into more reactive intermediates, have been described for a number of palladium mediated allylic substitution reactions.<sup>35,36</sup> We reasoned that in either case, it might prove possible to successfully realize the etherification reaction in the presence of structurally related activating agents, such as acetals and ketals, via a mixed acetal intermediate. The extension of this work to encompass a successful etherification procedure employing acetals or ketals would be a significant development, since a wide range of structurally diverse materials would be readily available for fine-tuning reactivity. Furthermore, while the use of orthoesters in FAlc etherification reactions provides a synthetic route with a much reduced energy requirement, an obvious limitation of this approach is the inability to regenerate the reactive species under the reaction conditions employed. Importantly, previous literature reports have demonstrated the facile formation of acetals and ketals directly from alcohols

employing zeolite and related mesoporous catalysts.<sup>31,37,38</sup> This would potentially lead to the development of an etherification route not only with greatly reduced energy requirements, but that would also display the additional benefit of significantly improved atom efficiency. With this exciting possibility in mind, we next studied the reactions of FAlc with acetals and ketals to assess their potential as promoters of the etherification reaction.

Initial reactions employing acetals proved encouraging, with benzaldehyde dimethyl acetal (BDMA, **7a**) providing moderate yields of **5b** under our standard reaction conditions, as did dimethyl acetals derived from p-tolualdehyde (p-Tol-DMA, **7b**) and p-anisaldehyde (p-Anis-DMA **7c**) Table 5, entries 1–3).

**Table 5: Etherification reactions of FAlc in the presence of acetals and ketals<sup>a</sup>**

$$\text{Furfuryl Alcohol (4)} \xrightarrow[\text{R}_1\text{CR}_2(\text{OCH}_3)_2, \text{ROH}]{\text{ZSM-5-(30) (20 mg), 40}^\circ\text{C}} \text{Furfuryl Ether (5a-b)}$$

Entry	ROH	Ketal	Conversion (mol%) <sup>b</sup>	Yield <b>5</b> (mol%) <sup>c</sup>	5a-b R = Et, Me		Mass Balance (mol%) <sup>d</sup>
					Humins (mol%)	Levulinate Esters (mol%)	
1	MeOH	<b>7a</b>	56	33	23	<5	77
2	MeOH	<b>7b</b>	28	20	8	<5	92
3	MeOH	<b>7c</b>	25	19	6	<5	94
4	MeOH	<b>8</b>	43	40	3	<5	97
5	MeOH	<b>8</b>	52	43	9	<5	91 <sup>e</sup>
6	MeOH	<b>8</b>	94	68	11	15	89 <sup>e,f</sup>
7	EtOH	<b>9</b>	17	17	0	<5	100
8	EtOH	<b>9</b>	44	36	3	5	97 <sup>e</sup>
9	EtOH	<b>9</b>	69	57	2	10	98 <sup>e,f</sup>
10	EtOH	<b>8</b>	32	24 <sup>g</sup>	8	<5	92
11	EtOH	<b>8</b>	40	32 <sup>g</sup>	3	5	97 <sup>f</sup>

<sup>a</sup>Experimental conditions: The catalyst was added to a solution of furfuryl alcohol (1 mmol) and ketal (1 mmol) in the specified solvent (1 mL) in a sealed reaction vessel and heated to 40 °C for 3 hours. <sup>b</sup>Quantity of FAlc consumed as determined by quantitative <sup>1</sup>H NMR spectroscopy of the crude reaction mixture. <sup>c</sup>Determined by quantitative <sup>1</sup>H NMR Spectroscopy and GC–MS analysis of the crude reaction mixture. <sup>d</sup>Sum of soluble materials identified by quantitative <sup>1</sup>H NMR spectroscopy and GC–MS analysis. <sup>e</sup>Reaction under concentrated conditions using 0.25 mL of solvent. <sup>f</sup>Reaction contains 40 mg catalyst. <sup>g</sup>Product is a 7:1 mixture of **5a/5b** by quantitative <sup>1</sup>H NMR analysis.

Presumably, the formation of the mixed acetal intermediate in these cases is slow given the relative stability of acetals, and further disfavoured in the presence of a large excess of methanol. We reasoned that switching to ketals, such as dimethoxy propane (DMOP, **8**), which undergo acetal exchange more rapidly might be beneficial,<sup>39</sup> and indeed in the presence of one equivalent of DMOP, FAlc underwent rapid etherification to produce MFE in high yield with little humin formation (entry 4). Carrying out the reaction under more concentrated conditions had little overall effect on the yield of **5b**, although a small decrease in mass balance was observed due to increased humin formation (entry 5). Increasing catalyst loading under concentrated reaction conditions led to almost complete consumption of the starting material giving high yields of **5b** with only moderate humin formation (entry 6). We next considered the reaction of FAlc with diethoxypropane (DEOP, **9**), which proved more sensitive to concentration, and under dilute reaction conditions, only low yields of **5a** were produced (entry 7). Carrying out the reaction under concentrated conditions led to significant improvements in both FAlc conversion and yields of **5a** at both low and high catalyst loadings (entries 8 and 9). It was also proved possible to carry out the corresponding telescoped reaction protocol employing DMOP in the presence of an excess of ethanol, to provide moderate yields of **5a** with good selectivity for the ethyl ester product (entries 10 and 11).

In conclusion, we have demonstrated that high yields of furfuryl ether bio-fuels are obtained in significantly improved yields to previously reported procedures by carrying out the etherification reaction in the presence of the commercially available ZSM-5 catalyst and an orthoester, such as TMOF and TEOF which is used as sacrificial reagent to aid formation of the intermediate furfuryl cation. These reactions proceed rapidly and efficiently at 40 °C with minimal formation of humins or products derived from hydrolysis. The observation that orthoester exchange occurs under the

reaction conditions led to the development of novel telescoped reaction procedures, employing TMOF in the presence of an excess of an alcohol solvent to provide the higher ether products **5a**, **5c** and **5d** in good yield and with good selectivity. Finally, we have extended this work to demonstrate that a novel etherification process can be developed employing acetals, and in particular ketals such as DMOP and DEOP, which are also efficient promoters of the etherification reaction, producing high yields of ether products in short reaction times with minimal humin formation. The use of acetals and ketals in place of orthoesters is particularly attractive given the wider range of structurally diverse acetals available, their ease of synthesis and the wider scope to regenerate the acetal species under the reaction conditions. Furthermore, we have also demonstrated that our telescoped reaction protocol can also be extended to encompass the reactions of DMOP with FAlc employing an excess of ethanol as solvent, to provide the corresponding ethyl ether product **5b** with high selectivity.

## **EXPERIMENTAL SECTION**

### **General Procedure for the Etherification of Furfuryl Alcohol with Ethanol in the Presence of TEOF**

The ZSM-5-(30) catalyst (20 mg) was added to a solution of furfuryl alcohol (98 mg, 1 mmol) and triethyl orthoformate (148 mg, 1 mmol) in ethanol (1 mL) in a sealed reaction vessel and heated to 40 °C for 2 hours. On completion of the reaction, the catalyst and insoluble polymeric products were removed by filtration through a Celite plug which was washed with deuterated chloroform (2 × 0.5 mL). Careful removal of the combined solvents under reduced pressure afforded the crude product as a colorless oil that was purified by column chromatography (hexane) gave the final product as a clear solution.<sup>13</sup>

### **General Procedure for the Sequential Orthoester Exchange-Etherification Reaction**

The ZSM-5-(30) catalyst (20 mg) was added to a solution of trimethyl orthoformate (104 mg, 1 mmol) in butanol (1 mL) in an open reaction vessel and heated to 60 °C for 90 minutes. The reaction was then cooled to room temperature and furfuryl alcohol (98 mg, 1 mmol) and an additional portion of catalyst (20 mg) were added. The reaction was then sealed, and heated to 40 °C for 2 hours. On completion of the reaction, the catalyst and insoluble polymeric products were removed by filtration through a Celite plug which was washed with deuterated chloroform (2 × 0.5 mL) and the crude reaction mixture was analysed by quantitative <sup>1</sup>H NMR analysis employing *para*-xylene as an internal standard.

### **General Procedure for the Tandem Orthoester Exchange-Etherification Reaction**

The ZSM-5-(30) catalyst (40 mg) was added to a solution of furfuryl alcohol (98 mg, 1 mmol) and trimethyl orthoformate (104 mg, 1 mmol) in butanol (1 mL) in a sealed reaction vessel and heated to 40 °C for 2 hours. On completion of the reaction, the catalyst and insoluble polymeric products were removed by filtration through a Celite plug which was washed with deuterated chloroform (2 × 0.5 mL) and the crude reaction mixture was analysed by quantitative <sup>1</sup>H NMR analysis employing *para*-xylene as an internal standard.

### **Notes**

The authors declare no competing financial interest.

### **ASSOCIATED CONTENT**

#### **Supplementary Information**

General methods, experimental procedures, catalyst characterization data and  $^1\text{H}$  NMR and GC–MS data for ether products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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## REFERENCES

- (1) Huber, G. W.; Iborra, S.; Corma, A. Synthesis of transportation fuels from biomass: chemistry, catalysis and engineering. *Chem. Rev.* **2006**, *106* (9), 10.1021/cr068360d.
- (2) Zhou, C.-H.; Beltramini, J. N.; Fan Y.-X.; Lu, G. Q. Chemoselective catalytic conversion of glycerol as a biorenewable source to valuable commodity chemicals. *Chem. Soc. Rev.* **2008**, *37* (3), 10.1039/b707343g.
- (3) Corma, A.; Iborra, S.; Velty, A. Chemical routes for the transformation of biomass into chemicals. *Chem. Rev.* **2007**, *107* (6), 10.1021/cr050989d.
- (4) Delidovich, I.; Hausoul, P. J. C.; Deng, Li.; Pfützeneuter, R.; Rose M.; Palkovits, R. Alternative monomers based on lignocellulose and their use for polymer production. *Chem. Rev.* **2016**, *116* (3), 10.1021/acs.chemrev.5b00354.
- (5) Gallezot, P. Conversion of biomass to selected chemical products. *Chem. Soc. Rev.* **2012**, *41* (4), 10.1039/c1cs15147a.
- (6) Hayes, D. J.; Fitzpatrick, S.; Hayes, M. H. B.; Ross, J. R. H. The Biofine Process – Production of Levulinic Acid, Furfural, and Formic Acid from Lignocellulosic Feedstocks. In *Biorefineries-Industrial Processes and Products: Status Quo and Future Directions*; ed. Kamm, B.; Gruber P. R.; Kamm, M., Eds.; Wiley-VCH, Weinheim, 2008.
- (7) Bohre, A.; Dutta, S.; Saha, B.; Abu-Omar, M. M. Upgrading furfurals to drop-in biofuels: an overview. *ACS Sustain. Chem. Eng.* **2015**, *3* (7), DOI: 10.1021/acssuschemeng.5b00271.

- (8) Lange, J.-P.; Price, R.; Ayoub, P. M.; Louis, J.; Petrus, L.; Clarke L.; Gosselink, H. Valeric biofuels: a platform of cellulosic transport fuels. *Angew. Chem. Int. Ed.* **2010**, *49* (26), 10.1002/anie.201000655.
- (9) Lange, J.-P.; van der Heide, E.; van Buijtenen, J.; Price, R. Furfural- A promising platform for lignocellulosic biofuels. *ChemSusChem* **2012**, *5* (1), 10.1002/cssc.201100648.
- (10) Dutta, S.; De, S.; Saha, B.; Alam, M. I. Advances in conversion of hemicellulosic biomass to furfural and upgrading to biofuels. *Catal. Sci. Technol.* **2012**, *2* (10), 10.1039/C2CY20235B.
- (11) Lange, J.-P. van der Graaf, W. D.; Haan, R. J.; Conversion of furfuryl alcohol into ethyl levulinate using solid acid catalysts. *ChemSusChem* **2009**, *2* (5), 10.1002/cssc.200800216.
- (12) Zhang, Z.; Dong, K.; Zhao, Z. Efficient conversion of furfuryl alcohol into alkyl levulinates catalyzed by an organic–inorganic hybrid solid acid catalyst. *ChemSusChem* **2011**, *4* (1), 10.1002/cssc.201000231.
- (13) Gonzalez Maldonado, G. M.; Assary, R. S.; Dumesic J.; Curtiss, L. A. Acid-catalyzed conversion of furfuryl alcohol to ethyl levulinate in liquid ethanol. *Energy Environ. Sci.* **2012**, *5* (10), 10.1039/C2EE22486K.
- (14) Kean, J. R.; Graham, A. E. Indium(III) triflate promoted synthesis of alkyl levulinates from furyl alcohols and furyl aldehydes. *Catal. Commun.* **2015**, *59*, 10.1016/j.catcom.2014.10.013.
- (15) Haan, R. J.; Lange, J.-P. Gasoline composition and process for the preparation of alkylfurfuryl ether. WO-2009/77606, **2009**.

- (16)Gao, X.; Peng, L.; Li, H.; Chen, K. Formation of humin and alkyl levulinate in the acid-catalyzed conversion of biomass-derived furfuryl alcohol. *Bioresources* **2015**, *10* (4), 10.15376/biores.10.4.6548–6564.
- (17)Bethell, D.; Graham, A. E.; Heer, J. P.; Markopoulou, O.; Page, P. C. B.; Park, B. K. Reactivity and selectivity in the oxidation of aryl methyl sulfides and sulfoxides by hydrogen-peroxide mediated by acetonitrile. *J. Chem. Soc., Perkin Trans. 2* **1993**, 10.1039/P29930002161.
- (18)Page, P. C. B.; Graham, A. E.; Park, B. K. A convenient preparation of symmetrical and unsymmetrical 1,2-diketones – application to fluorinated phenytoin synthesis. *Tetrahedron* **1992**, *48* (35), 10.1016/S0040-4020(01)88265-X.
- (19)Davies, T. E.; Kean, J. R.; Apperley, D. C.; Taylor S. H.; Graham, A. E. Dehydrative etherification reactions of glycerol with alcohols catalyzed by recyclable nanoporous aluminosilicates: telescoped routes to glyceryl ethers. *ACS Sustain. Chem. Eng.* **2016**, *4* (3), 10.1021/acssuschemeng.5b00894.
- (20)Davies, T. E.; Kean, J. R.; Apperley, D. C.; Taylor S. H.; Graham, A. E. Nanoporous aluminosilicate-mediated synthesis of ethers by a dehydrative etherification approach. *ACS Sustain. Chem. Eng.* **2014**, *2* (4), 10.1021/sc400492x.
- (21)Kumar, H. M. S.; Joyasawal, S.; Reddy, B. V. S.; Chakravarthy, P. P.; Krishna, A. D.; Yadav, J. S. Reactions of ortoesters with alcohols in the presence of acidic catalysts: a study. *Ind. J. Chem. B* **2005**, *44* (8) 1686–1692.

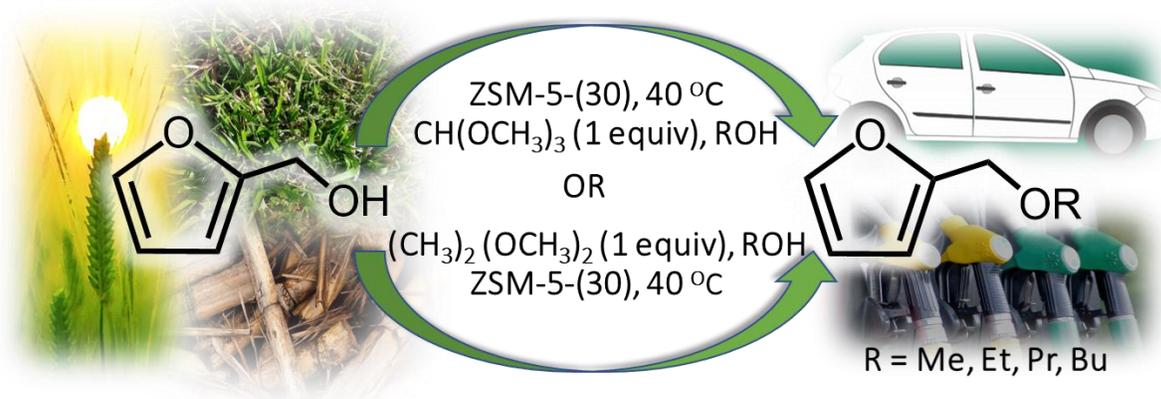
- (22) Lange, J.-P.; Otten, V. Dehydration of phenyl ethanol to styrene under reactive distillation conditions: understanding the catalyst deactivation. *Ind. Eng. Chem. Res.* **2007**, *46* (21), 10.1021/ie070397g.
- (23) Zhang, J.; Zhang, H.; Yang, X.; Huang, Z.; Cao, W. Study on the deactivation and regeneration of the ZSM-5 catalyst used in methanol to olefins. *J. Nat. Gas Chem.* **2011**, *20* (3), 10.1016/S1003-9953(10)60183-1.
- (24) Kim, T.; Assary, R. S.; Marshall, C. L.; Gosztola, D. J.; Curtiss L. A.; Stair P. C. Acid-catalyzed furfuryl alcohol polymerization: characterizations of molecular structure and thermodynamic properties. *ChemCatChem* **2011**, *3* (9), 10.1002/cctc.201100098.
- (25) Kim, T.; Assary, R. S.; Pauls, R. E.; Marshall, C. L.; Curtiss L. A.; Stair P. C. Thermodynamics and reaction pathways of furfuryl alcohol oligomer formation. *Catal. Commun.* **2014**, *46*, 10.1016/j.catcom.2013.11.030.
- (26) Ferrer, B.; Alvaro, M.; Garcia H.; Application of Dimethyl Carbonate as Solvent and Reagent. In *Green Solvents I: Properties and Applications in Chemistry*; Inamuddin, A. M.; Ed.; Springer, 2012.
- (27) Selva, M. Green approaches to highly selective processes: reactions of dimethyl carbonate over both zeolites and base catalysts. *Pure. Appl. Chem.* **2007**, *79* (11), 10.1351/pac200779111855.
- (28) Tietze, L. F. Domino reactions in organic synthesis. *Chem. Rev.* **1996**, *96* (1), 10.1021/cr950027e.

- (29) Wasilke, J. C.; Aubrey, S. J.; Baker, R. T.; Bazan, G. C. Concurrent tandem catalysis. *Chem. Rev.* **2005**, *105* (3), 10.1021/cr020018n.
- (30) Hayashi, Y. Pot economy and one-pot synthesis. *Chem. Sci.* **2016**, *7* (2), 10.1039/C5SC02913A.
- (31) Kubczyk, T. M.; Williams, S. M.; Kean, J. R.; Davies, T. E.; Taylor S. H.; Graham, A. E. Nanoporous aluminosilicate catalyzed Friedel–Crafts alkylation reactions of indoles with aldehydes and acetals. *Green Chem.* **2011**, *13* (9), 10.1039/C1GC15669A.
- (32) Tarabanko, V. E.; Chernyak, M. Y.; Simakova, I. L.; Kaigorodov, K. L.; Bezborodov, Y. N.; Orlovskaya, N. F. Antiknock properties of furfural derivatives. *Russ. J. Appl. Chem.* **2015**, *88* (11), 10.1134/S10704272150110063.
- (33) For detailed investigations on the formation of furfuryl alcohol cations and their subsequent reactions see: Choura, M.; Belgacem, N. M.; Gandini, A. Acid-catalyzed polycondensation of furfuryl alcohol: mechanisms of chromophore formation and cross-linking. *Macromolecules* **1996**, *29* (11), 10.1021/ma951522f.
- (34) Kim, T.; Assary, R. S.; Pauls, R. E.; Marshall, C. A.; Curtis, L. A.; Stair, P. C. Thermodynamics and reaction pathways of furfuryl alcohol oligomer formation. *Catal. Commun.* **2014**, *46*, 10.1016/j.catcom.2013.11.030.
- (35) Butt, N. A.; Zhang, W. Transition metal-catalyzed allylic substitution reactions with unactivated allylic substrates. *Chem. Soc. Rev.* **2015**, *44* (22), 10.1039/C5CS00144G.

- (36) Sundararaju, B.; Achard, M.; Bruneau, C. Transition metal catalyzed nucleophilic allylic substitution: activation of allylic alcohols via  $\pi$ -allylic species. *Chem. Soc. Rev.* **2012**, *41* (12), 10.1039/C2CS35024F.
- (37) Yip, L.; Kubczyk, T. M.; Davies, T. E.; Taylor, S. H.; Apperley D. C.; Graham, A. E. Nanoporous aluminosilicate mediated transacetalisation reactions: application in glycerol valorization. *Catal. Sci. Tech.* **2012**, *2* (11), 10.1039/C2CY20188G.
- (38) Thomas, B.; Prathapan, S.; Sugunan, S. Effect of pore size on the catalytic activities of K-10 clay and H-zeolites for the acetalization of ketones with methanol *Applied Catalysis A: General* **2004**, *277* (1–2), 10.1016/j.apcata.2004.09.017.
- (39) Moity, L.; Benazzouz, A.; Molinier, V.; Nardello-Rataj, V.; Elmkaddem, M. K.; de Caro, P.; Thiébaud-Roux, S.; Gerbaud, V.; Marione, P.; Aubry J.-M. Glycerol acetals and ketals as bio-based solvents: positioning in Hansen and COSMO-RS spaces, volatility and stability towards hydrolysis and autoxidation. *Green Chem.* **2015**, *17* (3), 10.1039/C4GC02377C.

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## Etherification Reactions of Furfuryl Alcohol in the Presence of Orthoesters and Ketals: Application to the Synthesis Furfuryl Ether Bio-Fuels



Recyclable ZSM-5 zeolites efficiently catalyze formation of furfuryl ether bio-fuels from furfuryl alcohol in the presence of orthoesters or ketals in novel, telescoped etherification reactions.