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Full Paper

Synthesis of Imines and Amines from Furfurals Using Continuous Flow Processing

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A simple procedure for the condensation of the bio-derived furfurals, 5-(methyl)furfural (MF) and 5-(chloromethyl) furfural (CMF), with primary amines is described herein. The experiments were conducted in both batch and flow conditions, with reaction times as short as 60 s. Moderately high temperatures were demonstrated to be suitable for the condensation reaction of MF in a few minutes whereas milder conditions and longer reaction times were necessary for CMF. Under these conditions the amine did not react with the methyl-chlorine group, leaving a very reactive site after condensation.

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Introduction

Over the past years, great attention has been devoted to finding alternative, renewable feedstocks to fossil oil for the production of biofuels and renewable industrial chemicals. In particular, high value added products from the fine chemicals, speciality chemicals, or pharmaceuticals sector allow for existing, fossil-based synthesis routes to be replaced by economic alternatives from renewable sources. Besides lignin-, fatty acid-, or terpene-based platforms, sugars constitute one of the major renewable feedstock classes which is of great interest for industrial chemical manufacture, including the production of fine chemicals, pharmaceuticals, fuels, and others.[1–7] Accessible through the dehydration reaction of cellulose and hemicellulose, sugars were demonstrated to be promising sources to form furan derivatives.[8,9] Furfural compounds such as 5-(hydroxymethyl)furfural (HMF), and 5-(chloromethyl) furfural (CMF) and their derivates levulinic acid (LA), levulinic esters, and γ-valerolactone (GVL) were particularly highlighted as precursors for bio-fuels, bio-fuel additives, and a range of different chemicals.[9–17] These platform molecules are targets or direct precursors to targets for further research and development according to the US Department of Energy.[18] HMF, LA, and GVL have been widely studied;[19] this is not the case for CMF. Reasons for this lower interest in CMF compared with HMF are believed to be: a) the need for a chlorine source to form CMF, its difficult isolation,[10,20] and its low stability over time under common storage conditions. However, the methyl-chlorine group enhances the reactivity of CMF compared with HMF, making it a relevant enough compound for implementing a sugar-based bio-refinery, provided it is reacted on shortly after synthesis. In 2011 our group reported a highly efficient dehydration of sugars to form CMF by biphasic continuous flow processing,[20] and included examples of various on-reactions of CMF to stable compounds. Pursuing the idea of expanding the existing pool of CMF derivatives, and building on procedures published by Cukalovic and Stevens,[21] we herein present a protocol for the synthesis of imines and amines from bio-derived furfural compounds. This class of compounds has reported attractive medical properties,[22–25] making it a source of potential candidates for further developments in the pharmaceutical and/or the speciality chemicals sectors.

Experimental

Materials and Analysis

The reagent CMF can be and was synthesized from a variety of different sugar feedstocks, including fructose, sucrose, glucose, and other sugar sources, using protocols for synthesis and purification reported in earlier work.[20] The reagents 5-(methyl)furfural (MF), hexylamine (HA), benzylamine (BA), aniline, and D-alanine methyl ester (AME, as the hydrochloride salt) were obtained from Sigma Aldrich; 40 % aqueous ammonia solution (NH_3(aq)) was provided by Chem-Supply Pty Ltd The solvents ethanol (EtOH), methanol (MeOH), dichloromethane (DCM), and acetone were obtained from Merck KGaA. All solvents and reagents with the exception of CMF were used without further purification. Reaction conversions were calculated from ^{1}H NMR spectra. Product compositions were analysed by gas chromatography–mass spectrometry (GC-MS); details for both can be found in the Supplementary Material.

Calculation of Space Time Yield

For the optimized continuous flow reactions presented in Table 1 (entries 3, 6 and 8), the conversion based space time yield (STY) of the reactor can be calculated based on the amount of product, m_p (based on conversion and calculated by NMR

Table 1. Reagents, reaction conditions, and results for the imination of furfurals with various amines

Entry	Method	Furfural	Amine	Solvent	Conc.[A] [mol/L]	T [°C]	t_R	Conv. [%]
1	Batch	MF	HA	EtOH	1.0	100	30 s	>99
2	Flow	MF	HA	EtOH	0.5	100	1 min	97
3	Flow	MF	HA	EtOH	1.0	100	1 min	>99
4	Batch	MF	BA	EtOH	1.0	100	1 min	98
5	Flow	MF	BA	EtOH	0.5	100	1 min	87
6	Flow	MF	BA	EtOH	1.0	100	1 min	94
7	Flow	MF	aniline	neat	–	140	20 min	81
8	Flow	MF	aniline	neat	–	140	40 min	93
9	Batch	MF	AME	MeOH	1.0	100	6 min	79
10	Batch	CMF	HA	DCM	1.0	100	20 min	–[B]
11	Batch	CMF	HA	EtOH	1.0	rt	16 h	98

[A]Concentration in mol of furfural per L of solvent; all reactions were carried out with 1.1 equivalents of amine.
[B]No clean conversion to the imine but a mixture of products was observed.

spectroscopy) using Eqn 1. This equation allows for easy comparison of the efficiency of batch and flow reactors.

$$\mathrm{STY} = \frac{m_p \cdot \dot{V}}{V_R \cdot V_{SS}} = \frac{m_p}{t_R \cdot V_R} \quad (1)$$

When calculating the STY in a continuous scenario, $\dot{V}$ is the total volumetric flow rate through the reactor, V_{SS} the combined volume of both stock solutions, and V_R the volume of the flow reactor. The equivalent calculation can be performed for batch reactors where t_R is the total processing time and V_R is the volume of the batch reaction vessel.

Batch Imination Reaction of MF

The following procedure is typical for the preparation of imines from MF and a series of different amines. A reactant solution of MF (220 mg, 2 mmol, 1 equiv.), amine (2.2 mmol, 1.1 equiv.), in EtOH (2 mL) (MeOH was used for reaction with AME), was premixed and filled into a sealed microwave vial. The reaction was conducted in a laboratory microwave reactor (Biotage Initiator) at 100°C with reaction times between 30 s and 20 min. A brown solution was obtained after the reaction, from which conversion was determined by ^{1}H NMR spectroscopy. For kinetic studies, small samples of the reaction mixture for ^{1}H NMR analysis were withdrawn through the septum of the glass vial using a syringe. For this the microwave reaction was stopped at various points in time over the course of the reaction, namely at 0.5, 1, 5, 10, and 20 min. Detailed reaction conditions and reagent compositions for each batch experiment can be found in Table 1.

Batch Imination Reaction of CMF

Initially, the same protocol as described above for the imination of MF was also applied to CMF, using the following reactant solution: CMF (314 mg, 2 mmol, 1 equiv.), HA (2.2 mmol, 1.1 equiv.), in DCM (2 mL); reaction temperature: 100°C; reaction time of 1 min. Due to unwanted side-reactions at 100°C, milder reaction conditions were chosen for CMF during later reactions: In a 50 mL round-bottom flask 1 g of CMF (7 mmol, 1 equiv.) and a large excess of $MgSO_4$ (~5 equiv.) were mixed with 15 mL of EtOH. Hexylamine (1.1 equiv.) was then added and the mixture was stirred for 21 h at room temperature. For kinetic studies using ^{1}H NMR spectroscopy, small samples of the reaction mixture were withdrawn using a syringe at various points in time over the course of the reaction, namely at 16 and 20.5 h.

Continuous Flow Imination of MF Using a Tubular Flow Reactor

The following procedure is typical for the preparation of imines from MF and a series of different amines in a tubular flow reactor. Two reactant solutions were prepared, one containing MF (5.96 mL, 60 mmol) in EtOH (24.04 mL), and the other containing HA (7.88 mL, 60 mmol), in EtOH (22.12 mL). The two solutions were continuously mixed in a T-piece and then fed into a Vapourtec R2/R4 flow reactor set-up, containing a 1.0 mm ID perfluoroalkoxy alkane (PFA) reactor coil (total reactor volume: 10 mL). The pump flow rate of the MF solution was set to 4.76 mL min^{-1}, and the pump flow rate of the HA solution was set to 5.24 mL min^{-1}. This resulted in a total flow rate of 10.00 mL min^{-1} and a reaction time of 1 min inside the two PFA reactor coils. The reaction was conducted at 100°C. The product, a transparent, orange solution, was collected at the reactor outlet, after passing through a 100 psi back pressure regulator. From this solution, the reaction conversion was determined by ^{1}H NMR analysis. After reaction, solvent was removed under reduced pressure, yielding a brown solid. Detailed reaction conditions and reagent compositions for each experiment in the tubular flow reactor can be found in Table 1. A schematic flow diagram of this reactor is shown in Fig. 1.

Batch Reduction of Furfural Imines to Amines

Sodium borohydride ($NaBH_4$, 1.5 equiv., 0.419 g) were added to the adduct solution of MF and HA in EtOH (see above). After stirring for 19 h at room temperature, the mixture was filtered over celite 545 and the resulting filtrate was concentrated under reduced pressure using a rotatory evaporator. Water (3 mL) was added, and the aqueous phase was extracted three times with 25 mL of DCM, and the organic layers combined altogether. Water was poured into the combined organic layers, and KCl was added to aid separation. The organic layer was isolated, dried over $MgSO_4$, and then filtered over celite 545. Solvent was removed under reduced pressure, yielding 1.238 g of product after drying.

Results and Discussion

The solution phase imination reactions presented herein follow the general reaction pathway shown in Scheme 1. The furfurals

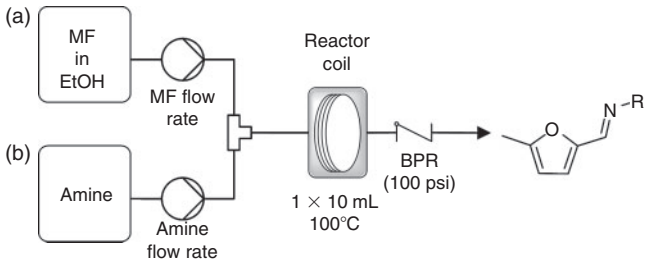
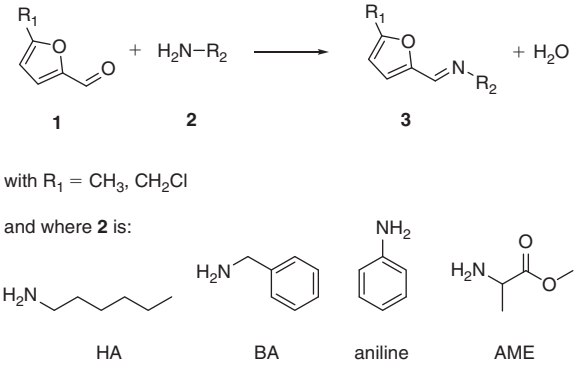


Fig. 1. Flow reactor configuration for the synthesis of furfural imines from MF and a variety of different amines.



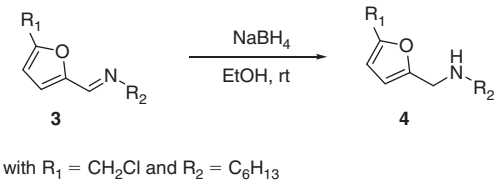
Scheme 1. Imination of furfurals, **1**, with various amines, **2**.

MF and CMF, **1**, were reacted with an amine, **2**, to form the corresponding imine, **3**. Different amines were subjected to this reaction including the aliphatic amines HA and BA, aniline, and the amino acid AME.

These experiments were carried out on a batch microwave reactor system or on a tubular continuous flow reactor (see experimental section) at temperatures between room temperature and 140°C, and reaction times between 30 s and 16 h. The results are presented in Table 1.

When reacting MF with an aliphatic amine (HA or BA, entries 1–6) at 100°C, the reaction reaches > 90 % conversion within one minute or less, in both batch and flow. Aniline reacts significantly slower, which can be explained by the aromaticity of the molecule. It is less prone to react through nucleophilic addition of the carbon from the aldehyde moiety; an observation which is in accordance with results from Cukalovic et al.[21] who found that there is a decreasing order of reactivity for amines: aliphatic amines > aromatic amines.

When applying the same forcing reaction conditions ($T \geq$ 100°C) to CMF, reaction of the amine with both the aldehyde and the chloromethyl group was observed, resulting in a mixture of products (entry 10). In order to selectively react only on the aldehyde moiety, milder reaction conditions were applied to CMF, yielding the desired imine product with high conversion after several hours (entry 11). In order to investigate the imination/amination reaction of CMF further, we reacted it with aqueous ammonia at room temperature, which resulted in a brown insoluble product. The, in parts, inconclusive analysis results from this reaction suggested that both the aldehyde functionality and the chloromethyl group reacted with ammonia to form an insoluble, potentially polymeric product (for further details see the Supplementary Material).



Scheme 2. Reduction of furfural imine to the corresponding amine.

As demonstrated herein, the reaction of furfurals with amines to the resulting imines can be fast and react to completion in minutes or seconds, if forcing reaction conditions are chosen. This requires the need for efficient heat management of the process on large scale, which can be readily achieved using continuous flow reactor technology. The emergence of compact continuous flow reactors has begun to transform the way chemical synthesis is conducted in research laboratories and small scale manufacturing over the past few years.[26–32] In several applications, where reaction times are short and heat management is important, intensified continuous processes inside tubular or plate-type flow reactors can successfully replace batch reactions classically carried out in stirred glass vessels. We have demonstrated the benefits of this superior heat management in previous work, including exothermic radical polymerizations in continuous flow,[33,34] the amination of aryl halides and esters,[35] or the flow synthesis of CMF.[20] The effective temperature control of a continuous flow reactor was also important for the intensification of the immination reaction of MF with aniline (entries 7 and 8). In comparison, the reaction of HMF with aromatic amines, performed in batch by Cukalovic and Stevens,[20] took 30 to 50 h at room temperature to achieve 83 to 97 % conversion, whereas we could achieve 93 % conversion at 140°C in only 40 min (entry 8), resulting in a space time yield of 1.3 kg L^{-1} h^{-1}. For the continuous flow imination of MF with HA (entry 3) we managed to achieve a STY of 11.5 kg L^{-1} h^{-1} and for the reaction with BA (entry 6) it was 11.2 kg L^{-1} h^{-1}. All three of these operations are attractive candidates for scale-up in industrial tubular flow reactors and are believed to result in efficient, intensified, continuous processes. These investigations are planned for future work.

As proof of concept for the reduction of the generated furfural imines to amines, one example, namely the adduct of CMF and HA (entry 11), was reacted with 1.5 equiv. of sodium borohydrate ($NaBH_4$) at room temperature (see Scheme 2). Full conversion into the corresponding secondary amine was observed. It is worth noting that the methyl-chlorine group was not reduced, leaving an extremely reactive site untouched and available for further reaction.

Conclusion

The condensation reaction between furfurals and amines was investigated using batch and continuous flow processing. It was shown that the synthesis of the corresponding imine was complete after only 1 min or less, when forcing conditions could be used, such as in the case of MF. Milder conditions are suitable for reactions with CMF, in order to selectively target the aldehyde group only, thus avoiding parallel amination on the chloromethyl moiety. When using continuous flow processing and elevated temperatures and pressures, the reaction with less reactive aniline could be performed in 40 min, which is a significant process intensification compared with classical batch processing.

Supplementary Material

Analytical procedures, the as-yet inconclusive results from the batch reaction of CMF with ammonia, and experimental data for entries 1, 4, 8, 9, 11 and Scheme 2 are available on the Journal's website.

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