Preparation of Sustainable Polar Aprotic Solvents from Biomass: One-Pot Two-Step Catalytic Reaction of Cellulose with N,N-Dimethylurea over Ru/C

Tayyebeh B. Champ[a], Shuo Liu[b], Benjamin L. Wegenhart[b], Tony Zhang*[c1], and Mahdi M. Abu-Omar*[a]

[a] Department of Chemistry and Biochemistry, University of California, Santa Barbara, Santa Barbara, CA, 93106, USA

[b] Department of Chemistry, Purdue University, West Lafayette, IN 47907, USA

[c] Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, USA

*Corresponding authors, email:

abuomar@chem.ucsb.edu

tony@tyligand.com

Abstract Inspired by innovative advancements in biomass valorization and the need for more environmentally benign polar aprotic solvents (PAS), a green and catalytic process is described for the synthesis of *N,N'*-dimethylimidazolidinone (DMI) and 1,3,4-trimethylimidazolidin-2-one (TMI) from cellulose, the most abundant and non-edible component of biomass. Notable properties of DMI and TMI include high boiling points, remarkable chemical stability, and being more eco-friendly than such frequently used PAS as dimethylformamide DMF. These properties make DMI and TMI appealing solvents for the pharmaceutical industry. Cellulose depolymerization and reaction of intermediate products with N,N-dimethylurea (DMU) to produce PAS have been investigated in a one-pot, two-step process at elevated temperatures. Ru/C is an effective multifunctional catalyst for both C-C bond cleavage in cellulose and subsequent hydrogenation of the unsaturated products. The catalyst also promotes the condensation of hydroxy ketone intermediates with DMU to create cyclic PAS. The tandem reactions are challenging because the varying conditions required in each step. An overall 85% selectivity for PAS was achieved starting from cellulose or sugar using DMI (the product) as a solvent. The optimized conditions for coupling of 1,2-propylene glycol (1,2-PG) with DMU was employed in a mechanistic study to produce PAS with both homogeneous and heterogenous Ru catalysts. Catalytic oxidation of 1,2-PG to hydroxy acetone is the key step to produce TMI and this step is promoted by electron-donating phosphine ligands on Ru.

Keywords: Renewable solvents, catalysis, glucose, fructose, imidazolidinone, retro-aldol, and glycolaldehyde

---

[1] Current affiliation: Tyligand Bioscience, Shanghai, China.

Introduction

Recently, significant effort has been directed to the development of green and sustainable procedures for the chemical conversion of non-edible biomass to high value-added compounds.[1-6] Environmentally benign solvents constitute an interesting target for bio-based products.[7-8] Examples of solvents from renewable sources include 2-methyltetrahydrofuran (2-MeTHF),[9-10] limonene,[11] ethanol,[12] and glycerol.[13] Although certain polar aprotic solvents (PAS) such as dimethylformamide (DMF) and dimethylacetamide (DMAc) are widely used in nucleophilic substitution reactions (nearly 50% of the PAS usage)[7, 14-15] and in the pharmaceutical industry,[7] these solvents (Figure 1) are not derived from renewable sources. While these are better solvents for a number of reactions because of their unique ability to dissolve polar materials and salts, they face growing scrutiny and regulatory restrictions as more concerns over their environmental impact and toxicity emerge.[8, 16] Newer PAS represented by cyclic urea *N,N′*-dimethylimidazolidinone (DMI) and *N,N′*-dimethylpropyleneurea (DMPU) have been used in place of DMF and DMAc with preliminary data indicating that they are safer for the endocrine system (Figure 1).[17] Considering the lack of PAS made from biomass, we sought to identify and develop environmentally friendly methods to produce sustainable PAS from renewable and non-edible bio-based resources.

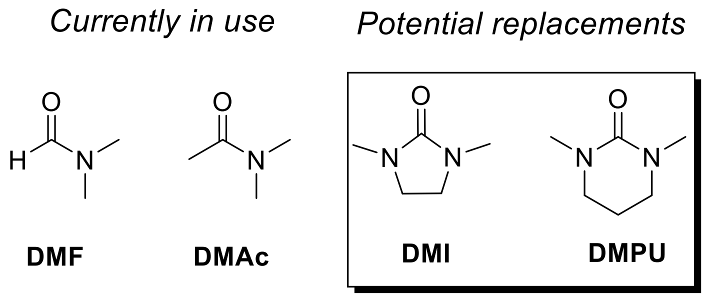
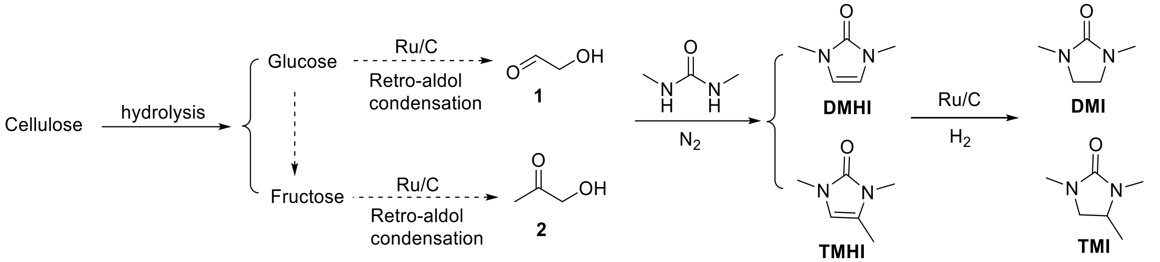


Figure 1. Industrially important Polar Aprotic Solvents (PAS). DMF and DMAc have reprotoxicity issues and are strongly regulated particularly by the European Union.[16] DMI and DMPU are considered more eco-friendly substitutes of DMF and DMAc.

Cellulose is one of the world's largest renewable, non-edible feedstock available with production of nearly 40 billion ton residues per year.[18] It is being considered as a promising alternative to petroleum and a sustainable resource to produce fuels and chemicals.[18-19] Catalytic conversion of cellulose into polyols including sorbitol, glycerol, ethylene glycol (EG) and 1,2-propylene glycol (1,2-PG) represents an important route for the effective utilization of cellulose.[4-5, 13, 18-19] Of particular interest for this work is the catalytic conversion of cellulose to short chain polyols (EG and 1,2-PG) and the coupling of these polyols with N,N-dimethylurea (DMU) to produce cyclic PAS such as *N,N′*-dimethylimidazolidinone (DMI) and 1,3,4-trimethylimidazolidin-2-one (TMI) (Scheme 1). Chemical stability and physical properties of DMI and TMI are suitable to serve as a high boiling PAS.[8, 20] For cellulose conversion to EG, there are three consecutive reactions: (1) hydrolysis of cellulose to glucose; (2) retro-aldol condensation of glucose to glycolaldehyde **1**; and (3) hydrogenation of glycolaldehyde to EG.[21-26] Cellulose conversion to hydroxyacetone **2** requires fructose undergone C-C bond cleavage via the retro-aldol reaction as shown in Scheme 1. Fructose can be produced either from direct cellulose hydrolysis or isomerization of glucose.[18, 22, 26] Water was recognized as the best solvent for cellulose conversion to short chain polyols. However, coupling of hydroxy ketones with urea has been investigated.[27-29] The synthesis of imidazolidinone derivatives from urea was achieved in high boiling organic solvents[28] or under microwave irradiation.[27] The coupling of diols, EG and 1,2-PG with DMU was first described in 1992 using tris(triphenylphosphine)ruthenium(II) chloride as catalyst;[30] nevertheless, no further study or development of this reaction has been reported. These reactions were conducted in refluxing diglyme EG and 1,2-PG for 12 hours giving a modest to good yields of 40% and 79%, respectively.



Scheme 1. Catalytic conversion of cellulose into polar aprotic solvent (PAS) via tandem catalysis.

The traditional approach of biomass valorization via platform molecules requires additional steps for the separation, purification, and drying of intermediates resulting in lower yield of the final products with a large amount of waste. A one-pot reaction is more promising for large-scale cellulose conversion to PAS. In this process, hydrolysis of cellulose, C-C bond cleavage of the sugars, coupling of hydroxy ketones **1** and **2** with DMU, and hydrogenation of the unsaturated products 1,3-dimethyl-1,3-dihydro-2H-imidazol-2-one (DMHI) and 1,3,4-trimethyl-1,3-dihydro-2H-imidazol-2-one (TMHI) occur in sequence to reach the maximum selectivity of the target products DMI and TMI (Scheme 1). The success of these tandem catalytic reactions in one-pot requires a multifunctional catalyst and a good solvent system. Ruthenium supported on activated carbon (Ru/C) is known for its high efficiency of cellulose conversion to EG and 1,2-PG[22] as well as its excellent reusability.[24] Solvent selection is challenging in this tandem reaction because of low cellulose conversion into hydroxy ketones **1** and **2** in organic solvents, whereas the highest yield for the reaction of hydroxy ketones with DMU are obtained in organic solvents.[27-28] To the best of our knowledge, there have been no reports until now to produce PAS from renewable resources. Herein, one-pot reactions of cellulose with DMU have been investigated in various solvents over Ru/C. The reaction proceeds efficiently in one-pot, two-step process. Reactions under N_2 atmosphere result in unsaturated intermediates **1** and **2** which upon coupling with DMU generate DMHI and TMHI. PAS is produced by hydrogenation of DMHI and TMHI in a second step in the same pot without a need for separation and purification of the intermediates. An overall 85% selectivity for PAS was achieved starting from cellulose or sugar (glucose/fructose). A mechanism that agrees with all experimental observations is also presented.

Results & Discussion

PAS from cellulose

A one-pot, two-step catalytic conversion of cellulose in the presence of DMU to PAS has been studied in various solvents at elevated temperature. Water is known to be an efficient medium for cellulose and sugar conversion to produce polyols using Ru/C catalyst under H_2 atmosphere.[4, 13, 18, 22] In our initial investigations, the reactions were performed in water under H_2 atmosphere resulting in little or no yield of PAS. Notably, performing the reaction under N_2 showed remarkably higher selectivity towards formation of unsaturated products, DMHI and TMHI, leading us to design this process as a one-pot, two-step cellulose conversion to PAS. The reaction was conducted under N_2 (35 bar) gas for 6 hours at 200 °C generating unsaturated PAS. After cooling down to room temperature and purging the N_2 gas, the reaction vessel was pressurized with H_2 gas to hydrogenate the unsaturated products in the same vessel in a second step.

Figure 2A provides an experimental schematic of the isolation and characterization of the products. Following the one-pot catalytic conversion and filtration of solid residues, the bio-oil-PAS mixture is fractioned into two forms for characterization and quantification of PAS and polyol derivatives. The PAS products are separated using High-Performance Liquid Chromatography (C18 preparative column), extracted with chloroform, and analyzed by various techniques as shown in Figure 2A. Product distribution of the reaction of diols with DMU were quantified by HPLC equipped with UV detector (HPLC/UV) at 210 nm. The HPLC chromatogram and the retention time associated with saturated and unsaturated PAS products are shown in Figure 2C. The polyol molecules including sorbitol, glycerol, 1,2-PG, and EG are analyzed by HPLC- Refractive Index Detector (HPLC/RID) at 70 °C.

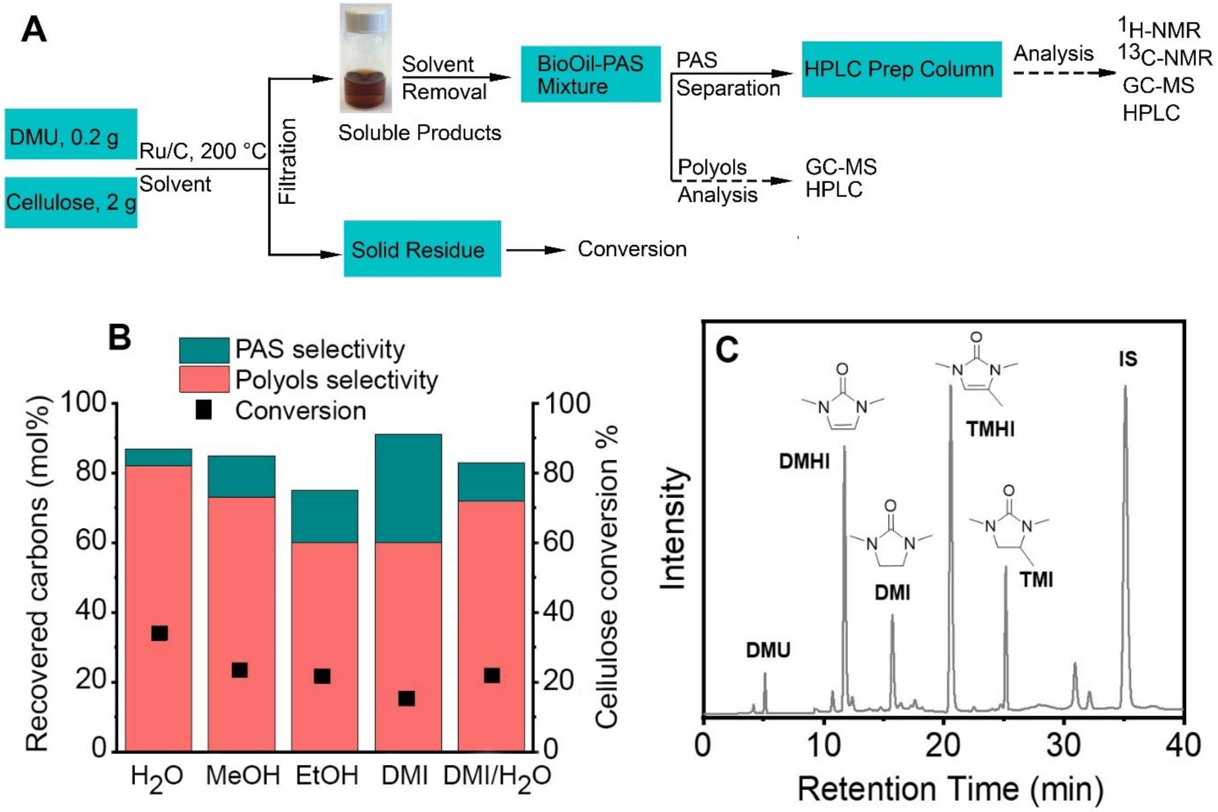


Figure 2. Cellulose conversion to PAS and polyols, the experimental schematic and mass balance. **(A)** Diagram showing the overall experimental procedure and analysis. **(B)** Cellulose conversions (■) in various solvents and mass balance accompanying the diagram shown in Figure 2A. Condition: Sigmacell cellulose (2.0 g), DMU (0.2 g, 2.23 mmol), Ru/C (0.2 g) with the corresponding solvent (20 mL) were heated in a 75 mL stainless steel autoclave at 200 °C in two steps: first, under N_2 atmosphere (35 bar) for 6 hours, then H_2 (30 bar) for 6 hours. DMI/H_2O (1:1 ratio) was used as solvent. **(C)** Exemplary HPLC chromatogram and retention time of the PAS products.

Cellulose conversions were determined by the change of cellulose weight before the reaction and after the solid residue (Figure 2A) was dried at 60 °C overnight (See Supporting Information for more details on calculation). Compositional analysis of the solid residue revealed that cellulose hydrolysis and its conversion to polyols and PAS compounds were less than 40% in various solvents (Figure 2B). In our optimized procedure, a large excess amount of cellulose (2.0 g) relative to DMU (0.2 g) is required to compensate for the low cellulose conversion. To investigate the role of the catalyst loading on cellulose depolymerization, the stainless-steel autoclave reactor was loaded with a high (0.4 g) or low (0.1 g) amount of Ru/C with 5 wt% Ru content in water, methanol, and DMI. Higher cellulose conversions were achieved at high catalyst loading without significant improvement on the yield of PAS products (Table S1).

However, as catalyst loading was decreased, cellulose conversions and PAS yields declined significantly indicating that the catalyst is necessary and responsible for cellulose cleavage. The reaction of cellulose with DMU in water was conducted at various temperatures. PAS selectivity increased significantly as the temperature increased from 150 (< 8%) to 180 °C (35%) and slightly improved at 200 °C (40%). Raising the temperature to 240 °C did not affect PAS selectivity.

As seen in Figure 2B under optimized conditions (0.2 g of Ru/C (5 wt%) at 200 °C), reactions in water gave the highest cellulose conversion (32%) because of higher solubility of cellulose in water at this temperature. Alcohols as organic hydrogen donor solvents gave lower cellulose conversion MeOH (23%), EtOH (20%) followed by DMI (13%) the lowest as an aprotic solvent. However, PAS selectivity from the reaction of small molecules with DMU is the lowest in water (5%) relative to organic solvents such as methanol (12 %), ethanol (15%) and DMI (31%). PAS was demonstrated to be the most selective in DMI as an aprotic solvent. The mass balance shows that above 80% moles of carbons from cellulose conversion were recovered in various forms of PAS and polyol products (Figure 2B and Table S2). On molar basis, only two carbons in DMI and three carbons in TMI are accounted for from cellulose. The missing mass, 9% in DMI up to 16% in DMI/water is presumably mostly volatile hydrocarbons, which were not analyzed in this study.

Product distribution of PAS derivatives and polyols selectivity are shown in Figure 3A-B, and also presented with more details in Table S2. The remaining DMU was measured by HPLC/UV at 210 nm to calculate DMU conversion and the selectivity for PAS derivatives (Figure 3A and Table S2). At 200 °C, most of DMU (~ 60%) is converted in two steps with DMI and TMI as the major products, likely due to the hydrogenation of unsaturated compounds DMHI and TMHI. Formation of DMHI and TMHI was verified by ^{1}H NMR and HPLC analysis from the reaction in ethanol. Overall, PAS selectivity is higher in the aprotic polar solvent DMI, than the protic solvents MeOH and EtOH, with the lowest amount in water. Side reaction of DMU with 2,3-butandiol resulted in formation of the byproduct 1,3,4,5-tetramethylimidazolidin-2-one with retention time at 32 minutes. (Figure 2C). However, this byproduct was not quantified.

Sorbitol (~ 20 %) is the major component of the polyol fraction along with ethylene glycol, 1,2-propylene glycol, and glycerol as shown in Figure 3B. Sorbitol is produced from hydrogenation of glucose and fructose in the second step under H_2.[18-19] EG and 1,2-PG are the results of hydrogenation of intermediates **1** and **2** respectively. Analysis on the remaining amount of EG (1.3 mmoles) and 1,2-PG (1.1 mmoles) after the second step in DMI revealed that significant amount of **1** and **2** are converted to the corresponding PAS products, 0.91 mmoles of DMI and 1.63 mmoles of TMI (Table S2). Therefore, improving the cellulose conversion to **1** and **2** would result in higher PAS yields.

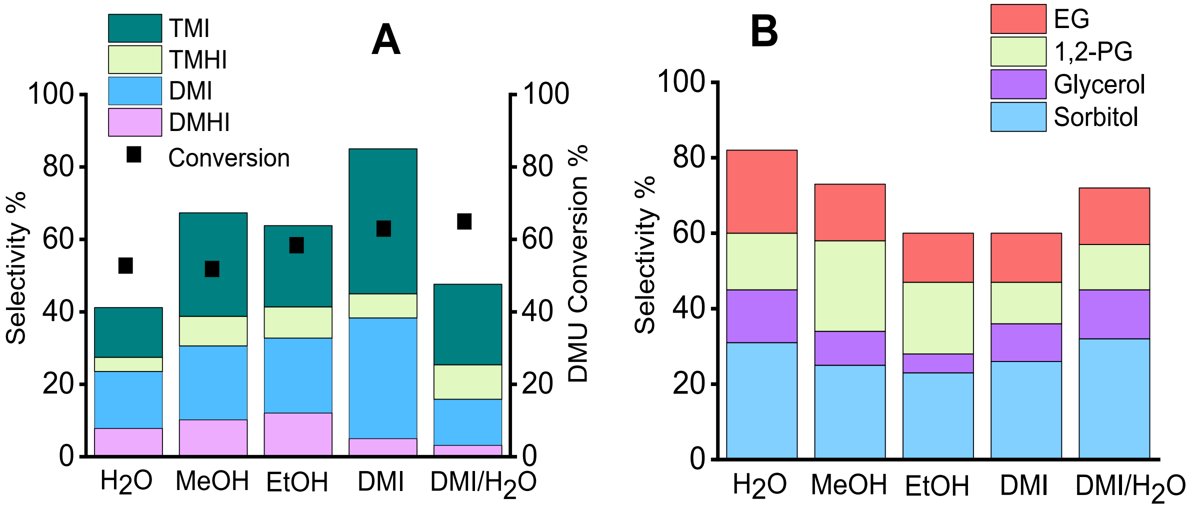


Figure 3. Analysis of PAS and polyol fractions from the catalytic conversion of cellulose in various solvents. (A) PAS fraction composition analyzed by HPLC-UV detection at 210 nm with benzyl alcohol solution (5.0 mM) as an internal standard. (B) Polyol fraction composition. Reaction conditions are identical to Figure 2B.

When various tungsten species such as tungsten trioxide (WO_3) or ammonium metatungstate (AMT) were used with Ru/C, higher cellulose conversion was achieved: WO_3 + Ru/C (65%), AMT + Ru/C (72%) in DMI. However, according to HPLC/UV analyses, the PAS yield was low. It has been reported that the C=C bonds such as those in the unsaturated PAS intermediates DMHI and TMHI can be cleaved in the presence of acidic tungsten species. Tungsten bronze (H_xWO_3) is the active species in catalytic tungsten-based systems known to promote cleavage of C-C bonds.[21-22, 25] Since acid catalyzes cellulose conversion as well as coupling of hydroxy ketones with DMU,[28] the addition of sulfuric acid in water (5mM solution) enhanced cellulose conversion to polyols in the presence of Ru/C; mainly ethylene glycol (33%) and sorbitol (45%) were obtained. However, it did not improve PAS yields, likely due to protonation of unsaturated intermediates **1** and **2** in acid. PAS yield strongly depends on cellulose depolymerization as well as the reaction medium. The reaction of glucose or fructose was investigated in various solvents to further understand the relationship between these intermediates with the production of PAS and elucidate the pertinent mechanism (Scheme 1).

Conversion of glucans directly to PAS

Sugar conversion was also studied in an autoclave under the optimized conditions in one-pot, two-steps process using Ru/C at 200 °C. After the second step under H_2 atmosphere, 100% of the sugar was converted to polyols and PAS products in both protic and aprotic solvents. The absence of glucose or fructose was confirmed by HPLC-reflective index detector (HPLC-RID) where excess amounts of polyols EG and 1,2-PG were detected (Figure 4 and Table S3). The polyol product distribution is consistent with previous results reported for sugar conversion.[4, 22]

The amount of DMU left in the reaction mixture was measured by HPLC-UV detection at 210 nm. The majority of DMU (between 70-80%) was converted to PAS (Figure 4A), which is higher than that observed for cellulose (~ 55-60 %, *vide supra*). The solvent effect on PAS selectivity followed a similar trend as what is observed for cellulose. The highest PAS selectivity was obtained in aprotic solvent DMI (> 80%). It decreased in protic solvents in EtOH (~ 70%), MeOH (~ 60%), with the lowest in water (approximately 40%). DMI is a better solvent choice because it affords high PAS selectivity. One of the interesting observations is that the higher selectivity of TMI was achieved from fructose whereas a higher selectivity of DMI was obtained from glucose conversion in both protic and aprotic solvents similar to what is predicted by retro-aldol condensation (Scheme 1). TMI was obtained in 61% selectivity from fructose vs. 26% selectivity from glucose in DMI (Figure 4A, Table S3). Reactions in water, methanol, and ethanol also verified this observation. Analysis of the polyol fractions revealed a higher selectivity of EG from glucose as well as a higher selectivity of 1,2-PG from fructose in both protic and aprotic solvents (Figure 4B). Catalytic conversion of fructose to 1,2-PG (32%) is significantly higher than EG (11%) over Ru/C catalyst in DMI. Glycolaldehyde **1** is likely the main intermediate of the glucose conversion to generate DMHI and the corresponding hydrogenated compound DMI (Scheme 1). **2** is the main intermediate from fructose leading to the production of TMHI and TMI. Reactions performed in one-step under hydrogen gas atmosphere suppressed PAS production, which is indicative of hydrogenation of hydroxy ketones **1** and **2**, and as a result EG and 1,2-PG do not react with DMU.

In a mass balance calculation, 80-88% moles of carbon from sugar conversion were recovered as PAS and polyol products (Figure 4B and Table S3). Two carbons in DMI and three carbons in TMI were accounted from the sugar molecule. The missing mass was due to 1,3,4,5-tetramethylimidazolidin-2-one and volatile hydrocarbons byproducts; however, these were not large enough to justify extensive effort to quantify them in this study.

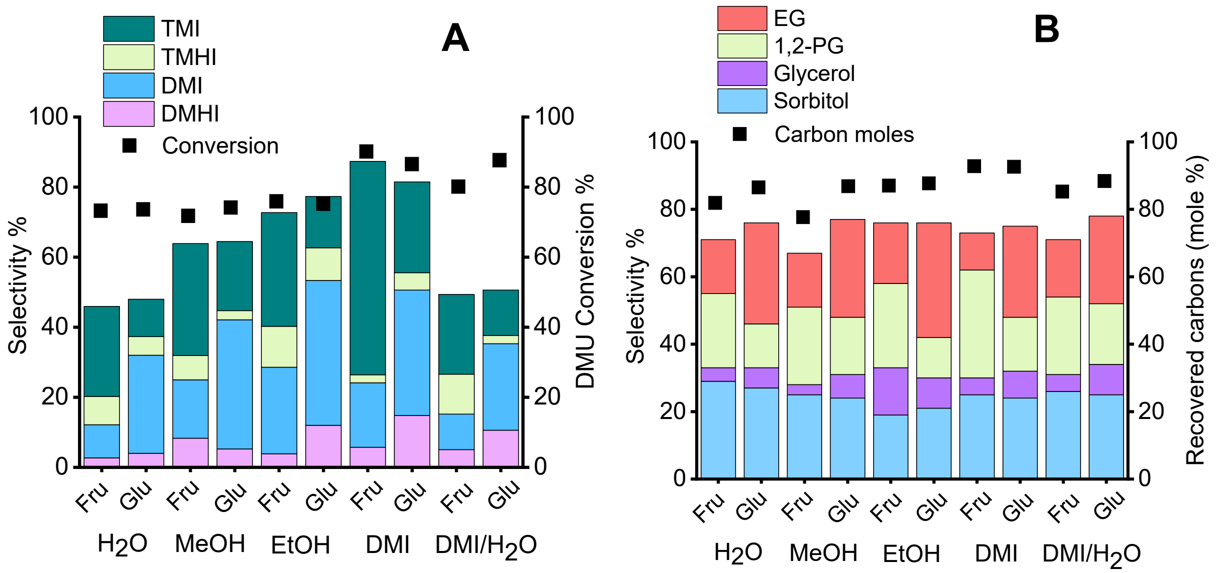


Figure 4. Analysis of PAS and polyol products obtained from the catalytic conversion of fructose (Fru) and glucose (Glu) in various solvents. **(A)** PAS products in various solvents. Selectivity was calculated based on the DMU conversion using HPLC/UV at 210 nm with benzyl alcohol solution (5.0 mM) as an internal standard. **(B)** Polyol selectivity and the molar mass balance of carbons from sugar conversion. Sugar conversion is 100% in all solvents. Conditions: sugars (1.0 g), DMU (0.2 g, 2.23 mmol), Ru/C (0.1 g) in various solvents (20 ml) were heated in a 75 ml stainless steel autoclave at 200 °C in two steps: first, under N_2 atmosphere (35 bar) for 6 hours, then H_2 (30 bar) for 6 hours. Ru/C catalyst contains 5 wt% Ru on activated carbon. DMI/H_2O (1:1 ratio) was used as a solvent.

Because of the different positions of the C=O group in glucose and fructose, glucose was primarily converted to **1** to form EG while fructose produced **2** under N_2 and ultimately hydrogenated to 1,2-PG under H_2 atmosphere.[22-23, 31-33] Due to the lack of stability of **1** and **2** at room temperature and the better overall yield of PAS from fructose, the coupling of 1,2-PG instead of hydroxyacetone with DMU was investigated.

Coupling of 1,2-PG with DMU and solvent effects

In a parallel study to further understand the catalytic conversion of polyols to PAS, reactions between 1,2-PG and DMU were performed under either N_2 or H_2 atmosphere at 200 °C (Table 1). Coupling of 1,2-PG and DMU mainly produces TMHI (above 80% yield) in organic solvents such as toluene, 2-MeTHF, and DMI under N_2 in one-step (Table 1B). Lower yields were obtained in protic solvents such as MeOH (59%) and Ethanol (65%) with the lowest in water (37%). These results are comparable to those previously obtained in two-step reactions for cellulose and sugar conversion (see above). The yield of coupling of 1,2-PG and DMU was significantly low (< 14%) under H_2 atmosphere (Table 1C). Two hypotheses are put forward to rationalize this observation: either the catalyst is fully hydrogenated resulting in the loss of catalytic activity or hydrogenation of hydroxyacetone **2**, the anticipated intermediate, shifts the reaction towards reactants.

Performing these reactions in one-pot two-steps under identical conditions to reactions performed with cellulose and sugars verified formation of TMI (Table 1D). The results from various solvents were consistent with what were achieved from the cellulose and sugar conversions to PAS. Higher yields (> 81%) were obtained in organic solvents using toluene (86%), 2-MeTHF (81%), and DMI (85%) (Table 1D, entries 1-4). These yields are comparable to those previously reported using diglyme as a solvent.[30] Comparing the results from the reactions under N_2 atmosphere (Table 1B) and the two-step reaction (Table 1D), it is conceivable that hydrogenation of unsaturated PAS occurs in the second step under H_2 atmosphere. There are two main advantages of using DMI as a solvent in this reaction. First, the reaction can be conducted at atmospheric pressure because of the high boiling point of DMI, 225 °C[34] (Table 1, entry 4). Second, the product of the reaction can serve as a solvent dissolving the reactants as the reaction proceeds. TMI was obtained in high yield (78%) using minimal amount of DMI as a solvent under identical conditions to entry 4, Table 1. The reaction yield is lower in protic solvents MeOH (63 %), EtOH (70%), and water (47%). In previous scanning tunneling microscope (STM) studies, adsorption of water on Ru surfaces results in various surface species such as molecular H_2O, H_2O-C complexes, H, O, OH species where the related reaction can occur on Ru surface.[35-36] It is likely that intermediate **2** is reduced to 1,2-PG in water or protic solvents preventing the coupling of **2** with DMU and hence PAS production.[27, 35-36]

Table 1. Coupling of 1,2-PG and DMU **(A).**

Entry	Solvent	**B** (TMHI %)	**C** (TMI %)	**D** (TMI %)
1	Toluene	88	14	86
2	2-MeTHF	86	11	81
3	DMI	84	12	85
4[e]	DMI	83	15	83
5	MeOH	59	4	62
6	EtOH	65	5	70
7	water	37	2	48

(A) 1,2-PG (1.7 g, 22.8 mmol), DMU (0.5 g, 5.7 mmol), 0.2 g Ru/C (5 wt%), and 20 mL solvent were heated in a 75 mL stainless steel autoclave at 200 °C. **(B)** One step reactions under N_2 (35 bar) for 12 hours. **(C)** Reactions under H_2 (30 bar) for 12 hours. **(D)** Two step reactions: first, under N_2 atmosphere (35 bar) for 6 hours, then H_2 (30 bar) for various times. Yields were analyzed by HPLC/UV with benzyl alcohol solution (5.0 mM) as an internal standard. TMHI Yields were also confirmed by ^{1}H-NMR with naphthalene as an internal standard (entries 1-4). [e]DMI under N_2 inert gas at 1 bar.

The product distribution was altered by varying the ratio of the starting materials under N_2 atmosphere (Table 2). Evidently, an increase of the 1,2-PG ratio leads to higher yields of TMHI, while the excess amount of DMU does not promote TMHI yields. Significant improvements on PAS yields were obtained when 1.5 ratio of 1,2-PG or higher was employed in this reaction (Table 2, entries 5-7). This effect is related to the higher rate of formation of **2** during the reaction. The reaction time can be halved to 6 hours by increasing the ratio of 1,2-PG to 2 times that of DMU (Table 2, entry 7), a comparable outcome to DMU conversion in the sugar study above (>70%). This indicates that a longer reaction time on the first step (under N_2) for the cellulose/sugar conversion would promote DMU conversion to PAS. To verify this observation, the reaction of cellulose with DMU was repeated under N_2 in EtOH for a longer time of 12 hours at 200 °C. Slightly higher DMU conversion (65% vs 58%) was achieved. It can be concluded that C-C bond cleavage and formation of **1** and **2** occurs faster than coupling of **1** and **2** with DMU in this catalytic cellulose or sugar conversion over the Ru/C catalyst.

Decreasing the amount of catalyst (0.1 g Ru/C) resulted in lower yield of TMHI (54%) under identical conditions as shown in entry 3, Table 2. The effect of temperature on the reaction was examined for the coupling of 1,2-PG with DMU under N_2 (Table S4). TMHI was obtained in 80% yield at 180 and 200 °C (Table S4, entries 4-5). Significantly lower yields (< 32%) were obtained at 150 °C and below. Performing this reaction under H_2 atmosphere instead of a two-step reaction resulted in a significant decline in PAS formation.

Table 2. Results of reactions with varying ratios of 1,2-PG and DMU.[a]

Entry	1,2-PG/DMU	Time (hour)	TMHI%	Remaining 1,2-PG%	Remaining DMU%
1	1 : 1	12	27	65	71
2	1 : 2	12	32	42	81
3	1.5 : 1	12	79	28	9
4	2 : 1	12	85	47	4
5	4 : 1	12	88	57	5
6	1.5 : 1	6	45	51	50
7	2 : 1	6	66	65	31
8	4 : 1	6	78	66	9

[a] 1 Equivalent of 1,2-PG (7.0 mmol), DMU (7 or 14 mmol), 0.2 g Ru/C (5wt%), and 2-MeTHF (20 ml) were heated in a 75 ml stainless steel autoclave under N_2 inert atmosphere (35 bar) at 200 °C. Yields and the remaining amount of 1,2-PG were analyzed by ^{1}H-NMR with naphthalene as an internal standard. The remaining amount of DMU was characterized by both ^{1}H-NMR and HPLC/UV detection.

Electronic effect of Ruthenium on the reaction of 1,2-PG and DMU

In order to understand how electronic variation on the Ru catalyst affects the reaction of 1,2-PG and DMU, experiments were conducted with homogeneous ruthenium catalysts generated *in situ*. These studies of a well-defined homogeneous system would elucidate electronic effects that can inform heterogeneous catalyst design. $RuCl_3 \cdot 3H_2O$ was combined with various arylphosphine ligands, in a 1:2 ratio, respectively. The catalyst mixtures were added in a microwave reactor to 1,2-PG and DMU in 2-MeTHF as a solvent under nitrogen atmosphere (details provided in Table S5). A linear is observed based on the TMHI yield vs. the Hammett constant of the para phenyl substituents (Figure 5).[37] Using triphenylphosphine, the yield of TMHI was only 38%. Adding an electron donating substituent to the phenyl ring increased the yield up to 61%. On the other hand, an electron withdrawing substituent dropped the yields to 20%. Therefore, higher electron density on Ru accelerates the rate of reaction for coupling 1,2-PG and DMU.

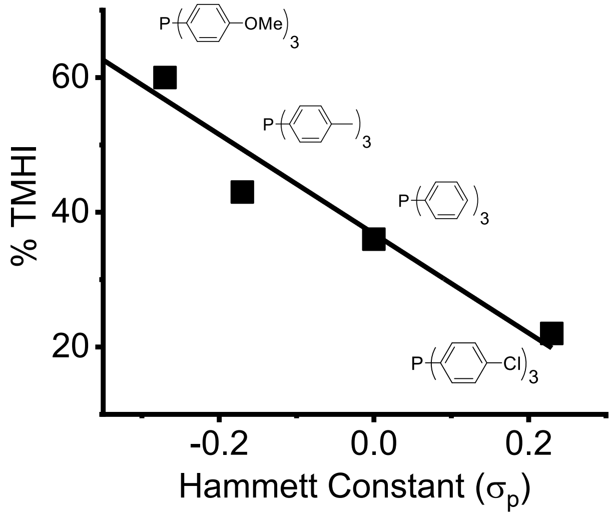


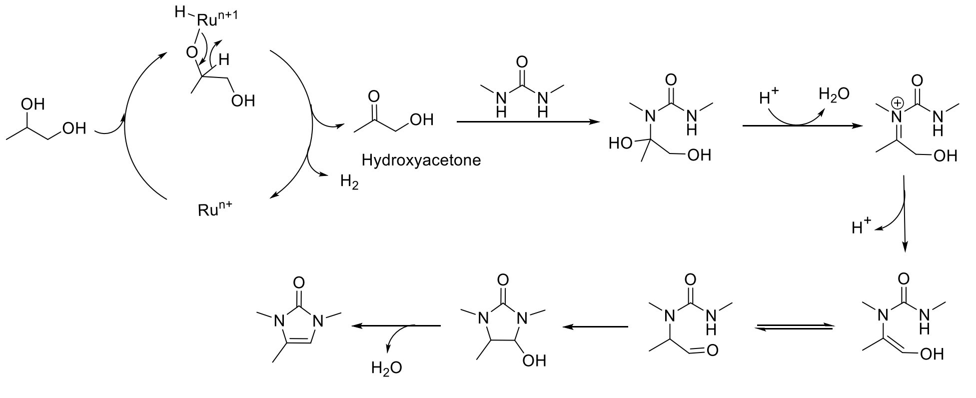
Figure 5. Plot of TMHI yields vs. Hammett constants of various para substituents on the phenyl phosphine ligands.

Discussion

A novel, direct, catalytic, and green process to obtain polar aprotic solvents (PAS) from renewable resources was described. PAS can be successfully produced in high selectivity in one-pot catalytic reactions of cellulose or sugars with DMU under Ru/C at 200 °C in two steps. The first step was conducted under N_2 atmosphere to yield the unsaturated PAS including DMHI and TMHI. Formation of DMHI and TMHI were verified in ethanol by ^{1}HNMR and HPLC-UV detection. The initial hypothesis was that the first step consists of two consecutive reactions, cellulose or sugar conversion to hydroxy ketones and their subsequent condensation reaction with DMU. Glucose and fructose break down into glycolaldehyde **1** and hydroxyacetone **2** respectively according to retro-aldol condensation.[25-26] The condensation of **1** and **2** intermediates with DMU creates DMHI and TMHI respectively. Experimentally, higher selectivity of DMI was obtained from the reactions of glucose with DMU in various solvents, while the selectivity of TMI was higher from analogous reactions starting from fructose. All supports the acyloins character of the intermediate species involved in the reaction pathway. In the second step, hydrogenation of DMHI and TMHI was conducted in the same pot over Ru/C under H_2 atmosphere.

A simpler system composed of vicinal diols and DMU to produce PAS proceeds through the catalytic oxidation of vicinal diols to the corresponding acyloins over RU/C as previously reported by Watanabe.[30] **2** is identified by ^{1}HNMR as the product of the catalytic oxidation of 1,2-PG by homogeneous or heterogeneous ruthenium catalysts in 2-MeTHF in the absence of DMU (SI-III) which provides further evidence for formation of hydroxy ketone **2** in the reaction pathway. Upon coordination of diols to Ru, the corresponding adduct intermediate undergoes β-hydride elimination releasing the acyloin product and an equivalent of hydrogen as illustrated in Scheme 2. The reaction of EG with DMU under the same conditions produced DMI at a lower yield (22%) indicating that oxidation of the secondary alcohol proceeds faster than the primary alcohol over Ru/C.

Various studies have documented the condensation reactions between acyloins and urea for preparation of 4-imidazolin-2-one derivatives by refluxing the mixture in a solvent in the absence of a catalyst.[27-28] In some cases, an acid or a base was used as a catalyst. Performing the reaction of **2** with DMU in the absence of a catalyst gives a yield of TMHI (69%) comparable to the catalytic reaction. Therefore, Ru/C is not required for the reaction of **2** with DMU. Once **2** is generated by catalytic oxidation of 1,2-PG over Ru/C, the condensation step proceeds thermally with an amine from DMU reacting with the carbonyl group of hydroxyacetone, forming enamine after dehydration and rearrangement. Upon tautomerization, enamine gives another carbonyl that can react with the second amine in a similar manner. The product TMHI is then obtained following a second dehydration (Scheme 2).



Scheme 2. Plausible mechanism for the production of unsaturated product TMHI

Finally, it should be noted that a two-step reaction allows the hydroxy-ketone/aldehyde intermediates **1** and **2** to react with DMU under N_2 in the first step when starting with cellulose or sugar. These intermediates (**1** and **2**) along with imine and enamine can easily undergo hydrogenation in the presence of Ru/C catalyst under H_2 atmosphere inhibiting production of the desired PAS, necessitating two-steps, first under N_2 to form unsaturated PAS followed by step two under H_2 to give the desired PAS products.

Conclusions

A green and catalytic approach for the conversion of cellulose, glucose, or fructose to polar aprotic solvents (PAS) is presented using Ru/C at 200 °C. Cellulose and sugar conversion follows a pattern predicted by retro-aldol mechanism with glycolaldehyde **1** and hydroxyacetone **2** being the major intermediates in route to PAS.[22-23, 25-26] Ru/C is an effective multifunctional catalyst where C-C bond cleavage of cellulose and sugars, oxidation of EG and 1,2-PG to **1** and **2** followed with coupling to DMU, and hydrogenation of the unsaturated PAS products were achieved in one-pot two-step reactions. One of the appealing aspects of this reaction chemistry is that the product of the reaction can serve as the solvent. This provides an attractive design element for a greener process not requiring an external solvent and its associated recycling costs. PAS in general (DMI in this study) is the best solvent to generate PAS at atmospheric pressure because of its high polarity and boiling point which adds another aspect to sustainability and safety by not needing high pressure reactors. The overall high PAS selectivity of 85% was achieved in one-pot, two-step process for both cellulose and sugar conversion over Ru/C at 200 °C.

Coupling of 1,2-PG with DMU using Ru/C catalyst provide a novel synthetic design to yield the imidizolone TMHI which upon hydrogenation gives the imidizolidinone TMI, an appealing compound worthy of further study as a solvent. Oxidation of diol to the corresponding acyloins is the key step for this reaction catalyzed by Ru/C. TMI was obtained in 80% yield in two-steps under heterogeneous catalysis in organic solvents with only hydrogen and water as the byproducts. Electronic effects from an *in situ* prepared homogeneous Ru phosphine catalysts revealed that electron-donating phosphine ligands (i.e. higher electron density on Ru) accelerated the reaction, 1,2-PG oxidation to hydroxyacetone. Further studies on the design of a Ru catalyst using different supports should provide more effective catalysts for C-C cleavage of carbohydrates and oxidation of vicinal diols to improve the productivity of PAS from renewable sources.

Experimental section

Material 1,2-Propylene glycol and D-(-)-Fructose were purchased from Acros-Organics. D-(+)-Glucose was purchased from Alfa-Aesar. Ruthenium (5wt%) supported on activated carbon (Ru/C), sigmacell cellulose, and all other chemicals were purchased from Sigma Aldrich. Naphthalene, benzyl alcohol, and cis-1,5-cyclooctane diol from

Sigma-Aldrich was used as an internal standard for ^{1}H-NMR, and HPLC/UV, and HPLC/RID respectively. All chemicals were used as received without further purification.

General procedure

A 75 mL stainless steel autoclave reactor from Parr Instruments was charged with the substrates, Ru/C, and a glass magnetic stir bar. Prior to the reaction, the autoclaves were flushed three times with nitrogen before applying 35 bars of nitrogen pressure and heating to 200 °C. After termination of the reaction periods, the autoclaves were cooled down, released the nitrogen pressure, and charged with 35 bars of hydrogen gas conducting the hydrogenation step at 200 °C. The reaction conditions are described under the table footnote. Following the one-pot catalytic conversion, the reaction mixture is fractioned into two forms, PAS derivatives that are analyzed by High-Performance Liquid Chromatography equipped with a UV detector (HPLC/UV) and the polyol molecules analyzed by a HPLC- Reflective Index Detector (HPLC/RID). Details on characterization methods are provided in the Supporting Information. Cellulose conversion was determined by the weight difference of cellulose before and after the reaction; product selectivities were calculated on the DMU basis for one-pot, two-step experiments.

In homogeneous catalytic reactions, catalyst $RuCl_3\cdot 3H_2O$ and the respective phosphine ligands were added to the reaction vessel along with DMU, 1,2-PG, and 2-MeTHF solvent. After briefly sparging with inert N_2 gas, the reaction vessel was sealed and heated at 180 °C. Microwave reactions were performed using a CEM Discover SP System and a standard heating method with a set point of 180°C (reaction temperature determined by a vertically focused IR temperature sensor).

Supporting Information

The Supporting Information is available free of charge online.

Product characterization for TMI and TMHI, HPLC and NMR analyses, effect of catalyst loading, mass balance tables, temperature dependence, and effect of phosphine ligands.

Acknowledgements

This research was supported by grants from Eli Lilly and the National Science Foundation (CHE-1856753). We thank Dr. Hao Luo, Dr. Baoyuan Liu, and Mr. Manhao Zeng for their assistance with HPLC analyses and helpful discussions.

Abbreviations

PAS	polar aprotic solvent
DMI	N,N'-dimethylimidazolidinone
DMHI	1,3-dimethyl-1,3-dihydro-2H-imidazol-2-one
TMI	1,3,4-trimethylimidazolidin-2-one

TMHI	1,3,4-trimethyl-1,3-dihydro-2H-imidazol-2-one
2-MeTHF	2-methyltetrahydrofuran
1,2-PG	1,2-propylene glycol
EG	ethylene glycol
DMU	N,N’-dimethylurea
Ru/C	ruthenium supported on activated carbon
HPLC	high performance liquid chromatography
RID	refractive index detector
GC	gas chromatography

References

1. Dhepe, P. L.; Fukuoka, A., Cellulose conversion under heterogeneous catalysis. *ChemSusChem: Chemistry & Sustainability Energy & Materials* **2008,** *1* (12), 969-975. DOI: 10.1002/cssc.200800129
2. Climent, M. J.; Corma, A.; Iborra, S., Heterogeneous catalysts for the one-pot synthesis of chemicals and fine chemicals. *Chem. Rev.* **2011,** *111* (2), 1072-133. DOI: 10.1021/cr1002084
3. Mascal, M.; Nikitin, E. B., Direct, High-yield conversion of cellulose into biofuel. *Angew. Chem.* **2008,** *120* (41), 8042-8044. DOI: 10.1002/anie.200801594
4. Ji, N.; Zhang, T.; Zheng, M.; Wang, A.; Wang, H.; Wang, X.; Chen, J. G., Direct catalytic conversion of cellulose into ethylene glycol using nickel-promoted tungsten carbide catalysts. *Angew. Chem. Int. Ed. Engl.* **2008,** *47* (44), 8510-8513. DOI: 10.1002/anie.200803233
5. Corma, A.; Iborra, S.; Velty, A., Chemical routes for the transformation of biomass into chemicals. *Chem. Rev.* **2007,** *107* (6), 2411-2502. DOI: 10.1021/cr050989d
6. Satari, B.; Karimi, K.; Kumar, R., Cellulose solvent-based pretreatment for enhanced second-generation biofuel production: a review. *Sustainable energy & fuels* **2019,** *3* (1), 11-62. DOI: 10.1039/C8SE00287H
7. Ashcroft, C. P.; Dunn, P. J.; Hayler, J. D.; Wells, A. S., Survey of Solvent Usage in Papers Published in Organic Process Research & Development 1997–2012. *Organic Process Research & Development* **2015,** *19* (7), 740-747. DOI: 10.1021/op500276u
8. Lo, C. C.; Chao, P. M., Replacement of carcinogenic solvent HMPA by DMI in insect sex pheromone synthesis. *J. Chem. Ecol.* **1990,** *16* (12), 3245-3253. DOI: 10.1007/BF00982095
9. Pace, V.; Hoyos, P.; Castoldi, L.; Dominguez de Maria, P.; Alcantara, A. R., 2-Methyltetrahydrofuran (2-MeTHF): a biomass-derived solvent with broad application in organic chemistry. *ChemSusChem* **2012,** *5* (8), 1369-1379. DOI: 10.1002/cssc.201100780
10. Al-Shaal, M. G.; Dzierbinski, A.; Palkovits, R., Solvent-free γ-valerolactone hydrogenation to 2-methyltetrahydrofuran catalysed by Ru/C: a reaction network analysis. *Green Chemistry* **2014,** *16* (3), 1358-1364. DOI: 10.1039/C3GC41803K
11. Lopresto, C. G.; Petrillo, F.; Casazza, A. A.; Aliakbarian, B.; Perego, P.; Calabrò, V., A non-conventional method to extract D-limonene from waste lemon peels and comparison with traditional Soxhlet extraction. *Sep. Purif. Technol.* **2014,** *137*, 13-20. DOI: 10.1016/j.seppur.2014.09.015

12. Jalbert, J.; Duchesne, S.; Rodriguez-Celis, E.; Tétreault, P.; Collin, P., Robust and sensitive analysis of methanol and ethanol from cellulose degradation in mineral oils. *J. Chromatogr. A* **2012,** *1256*, 240-245. DOI: 10.1016/j.chroma.2012.07.069

13. Luo, C.; Wang, S.; Liu, H., Cellulose Conversion into Polyols Catalyzed by Reversibly Formed Acids and Supported Ruthenium Clusters in Hot Water. *Angew. Chem.* **2007,** *119* (40), 7780-7783. DOI: 10.1002/anie.200702661

14. Bhuvaneshwari, D. S.; Elango, K. P., Solvent hydrogen bonding and structural effects on nucleophilic substitution reactions: Part 4 — Reaction of 2-chloro-5-nitropyridine with para-substituted anilines in acetonitrile/dimethylformamide mixtures. *J. Mol. Liq.* **2008,** *143* (2-3), 147-153. DOI: 10.1016/j.molliq.2008.07.008

15. Mancini, P. M. E.; Terenzani, A.; Adam, C.; Pérez, A.; Vottero, L. R., Characterization of solvent mixtures. Part 8 — preferential solvation of chemical probes in binary solvent systems of a polar aprotic hydrogen-bond acceptor solvent with acetonitrile or nitromethane. Solvent effects on aromatic nucleophilic substitution reactions. *J. Phys. Org. Chem.* **1999,** *12* (3), 207-220. DOI: 10.1002/(sici)1099-1395(199903)12:33.0.co;2-w

16. Dunn, P. J., The importance of green chemistry in process research and development. *Chem. Soc. Rev.* **2012,** *41* (4), 1452-1461. DOI: 10.1039/C1CS15041C

17. Laird, T., Green Chemistry is Good Process Chemistry. *Organic Process Research & Development* **2012,** *16* (1), 1-2. DOI: 10.1021/op200366y

18. Liu, X.; Wang, X.; Yao, S.; Jiang, Y.; Guan, J.; Mu, X., Recent advances in the production of polyols from lignocellulosic biomass and biomass-derived compounds. *RSC Adv.* **2014,** *4* (90), 49501-49520. DOI: 10.1039/C4RA06466F

19. Fukuoka, A.; Dhepe, P. L., Catalytic conversion of cellulose into sugar alcohols. *Angew. Chem. Int. Ed. Engl.* **2006,** *45* (31), 5161-5163. DOI: 10.1002/anie.200601921

20. Takaragi, A.; Minoda, M.; Miyamoto, T.; Liu, H. Q.; Zhang, L. N., Reaction characteristics of cellulose in the LiCl/1, 3-dimethyl-2-imidazolidinone solvent system. *Cellulose* **1999,** *6* (2), 93-102. DOI: 10.1023/A:1009208417954

21. Zhang, J. Y.; Hou, B. L.; Wang, A. Q.; Li, Z. L.; Wang, H.; Zhang, T., Kinetic Study of the Competitive Hydrogenation of Glycolaldehyde and Glucose on Ru/C with or Without AMT. *AlChE J.* **2015,** *61* (1), 224-238. DOI: doi.org/10.1002/aic.14639

22. Liu, Y.; Luo, C.; Liu, H., Tungsten trioxide promoted selective conversion of cellulose into propylene glycol and ethylene glycol on a ruthenium catalyst. *Angew. Chem. Int. Ed. Engl.* **2012,** *51* (13), 3249-3253. DOI: 10.1002/anie.201200351

23. Sasaki, M.; Goto, K.; Tajima, K.; Adschiri, T.; Arai, K., Rapid and selective retro-aldol condensation of glucose to glycolaldehyde in supercritical water. *Green Chemistry* **2002,** *4* (3), 285-287. DOI: 10.1039/B203968K

24. Tai, Z.; Zhang, J.; Wang, A.; Zheng, M.; Zhang, T., Temperature-controlled phase-transfer catalysis for ethylene glycol production from cellulose. *Chem Commun (Camb)* **2012,** *48* (56), 7052-7054. DOI: 10.1039/C2CC32305B

25. Zhang, J.; Hou, B.; Wang, A.; Li, Z.; Wang, H.; Zhang, T., Kinetic study of retro-aldol condensation of glucose to glycolaldehyde with ammonium metatungstate as the catalyst. *AlChE J.* **2014,** *60* (11), 3804-3813. DOI: 10.1002/aic.14554

26. Wang, A.; Zhang, T., One-pot conversion of cellulose to ethylene glycol with multifunctional tungsten-based catalysts. *Acc. Chem. Res.* **2013,** *46* (7), 1377-1386. DOI: 10.1021/ar3002156

27. Feng, J.-C.; Meng, Q.-H.; Liu, Y.; Dai, L., Condensation Reaction of Acyloins with Urea without Solvent under Microwave Irradiation. *Org. Prep. Proced. Int.* **1997,** *29* (6), 687-689. DOI: 10.1080/00304949709355249

28. Kim, Y. B.; Kim, C. S.; Lee, C. K., Condensation-Reactions of Aryl Acyloins with Ureas in Ethylene-Glycol. *J. Heterocycl. Chem.* **1994,** *31* (6), 1653-1656. DOI: 10.1002/jhet.5570330403

29. Glasnov, T. N.; Kappe, C. O., Continuous-flow syntheses of heterocycles. *J. Heterocycl. Chem.* **2011,** *48* (1), 11-30. DOI: 10.1002/jhet.568

30. Kondo, T.; Kotachi, S.; Watanabe, Y., Ruthenium Complex-Catalyzed Synthesis of 1,3-Disubstituted 2,3-Dihydroimidazol-2-Ones from N,N'-Disubstituted Ureas and Vicinal Diols. *J Chem Soc Chem Comm* **1992,** (18), 1318-1319. DOI: 10.1039/C39920001318

31. Hayes, M. L.; Pennings, N. J.; Serianni, A. S.; Barker, R., Epimerization of Aldoses by Molybdate Involving a Novel Rearrangement of the Carbon Skeleton. *J. Am. Chem. Soc.* **1982,** *104* (24), 6764-6769. DOI: 10.1021/ja00388a047

32. Kabyemela, B. M.; Adschiri, T.; Malaluan, R. M.; Arai, K., Glucose and fructose decomposition in subcritical and supercritical water: Detailed reaction pathway, mechanisms, and kinetics. *Ind. Eng. Chem. Res.* **1999,** *38* (8), 2888-2895. DOI: 10.1021/ie9806390

33. Kabyemela, B. M.; Adschiri, T.; Malaluan, R. M.; Arai, K., Kinetics of glucose epimerization and decomposition in subcritical and supercritical water. *Ind. Eng. Chem. Res.* **1997,** *36* (5), 1552-1558. DOI: 10.1021/ie960250h

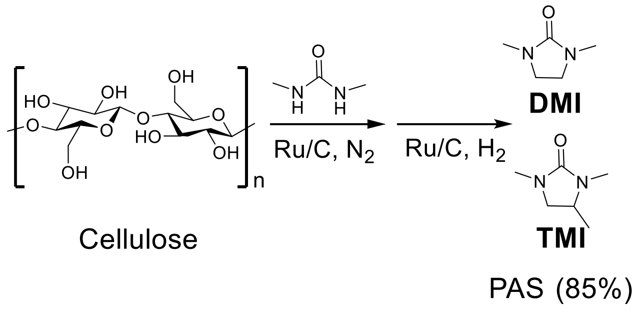
34. Endo, A.; Miyake, M.; Hirato, T., Electrodeposition of Aluminum from 1,3-Dimethyl-2-Imidazolidinone/AlCl3 baths. *Electrochim. Acta* **2014,** *137*, 470-475. DOI: 10.1016/j.electacta.2014.06.044

35. Chang, C.-R.; Huang, Z.-Q.; Li, J., The promotional role of water in heterogeneous catalysis: mechanism insights from computational modeling. *Wiley Interdisciplinary Reviews: Computational Molecular Science* **2016,** *6* (6), 679-693. DOI: 10.1002/wcms.1272

36. Shimizu, T. K.; Mugarza, A.; Cerdá, J. I.; Heyde, M.; Qi, Y.; Schwarz, U. D.; Ogletree, D. F.; Salmeron, M., Surface Species Formed by the Adsorption and Dissociation of Water Molecules on a Ru(0001) Surface Containing a Small Coverage of Carbon Atoms Studied by Scanning Tunneling Microscopy. *The Journal of Physical Chemistry C* **2008,** *112* (19), 7445-7454. DOI: 10.1021/jp711097j

37. Hansch, C.; Leo, A.; Taft, R. W., A Survey of Hammett Substituent Constants and Resonance and Field Parameters. *Chem. Rev.* **1991,** *91* (2), 165-195. DOI: 10.1021/cr00002a004

For Table of Contents Use Only



One-pot, two-step reaction for making renewable polar aprotic solvents (PAS) from cellulose; the reaction product is used as solvent.