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Organocatalyzed One-Step Synthesis of Functionalized *N*-Alkyl-Pyridinium Salts from Biomass Derived 5-Hydroxymethylfurfural

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Supporting Information

ABSTRACT: An efficient and scalable method has been developed for the synthesis of *N*-alkylpyridinium salts from biomass derived 5-hydroxymethylfurfural and alkyl amines using a catalytic amount of formic acid. This protocol is also extended to various diamines providing the exclusive formation of mono-*N*-alkylpyridinium salts. In addition, the mechanism for the formation of pyridinium salts was studied by DFT and using $H_2{}^{18}O$ isotope labeled experiments showing no incorporation of ^{18}O in the product.

Pyridinium salts (Pyr) are privileged scaffolds found in many natural and bioactive compounds.[1] Pyr containing natural products such as Njaoaminiums and Pachychalines are well-known for their wide occurrence in marine sponges of the Haplosclerida order.[2,3] In general, Pyr are known to exhibit many applications such as acylating agents, phase transfer catalysts, biocides such as antimicrobial agents, dyes, and cationic surfactants.[4] Moreover, they have high synthetic value as key intermediates for the production of a broad range of pharmacologically relevant piperidine as well as dihydro- and tetrahydropyridine frameworks.[5] Pyr that are liquid at room temperature, so-called "pyridinium ionic liquids",[4b] such as 1-alkylpyridinium salts, are potential solvents in synthesis and catalysis.[4b] The classical routes to synthesize Pyr involve the reaction of pyridine with organic halides or quaternization of the pyridine nitrogen using chloromethylalkyl ethers or sulfides.[4a] Current reports on the synthesis of Pyr by catalytic C–H activation[6] and the utility of pyridinium salts to originate conjugated dienals, a highly useful synthetic precursor for constructing natural products,[7] reveals the high demand of pyridinium salts in synthetic chemistry. Among them, 3-substituted pyridinium salts can be transformed with great effect for piperidine-3-ol/-one functionalization. For example, Zhou et al. recently reported an effective Ir-catalyzed hydrogenation of 3-hydroxy pyridinium salts to give piperidine-3-ones.[8] This class of salts is known to exhibit biological activity including cytotoxicity and ichthyotoxicity.[9] A few examples of pyridinium salts containing natural products are shown in Figure 1.

Several efforts have been successfully made in the construction of natural products on different core moieties using pyridinium salts as the key substrate. Figure 2 shows some examples of natural products synthesized using Pyr.

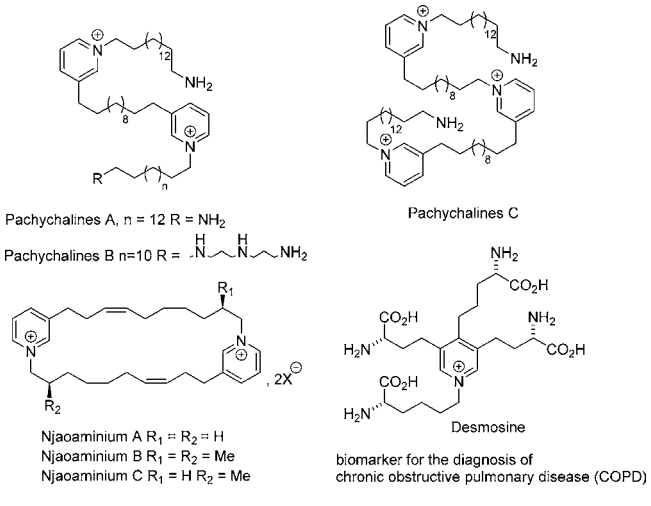

Figure 1. Natural products containing pyridinium salts.[10]

On the other hand, with the increasing demand for biorenewable resources as an alternative feedstock for the production of fuels and bulk chemicals,[12] 5-hydroxymethylfurfural (HMF) gained considerable attention, as it is derived from renewable resources such as fructose, glucose,, or cellulose. HMF acts as a bridging molecule linking biomass to fuels and chemicals and is also very useful for the production

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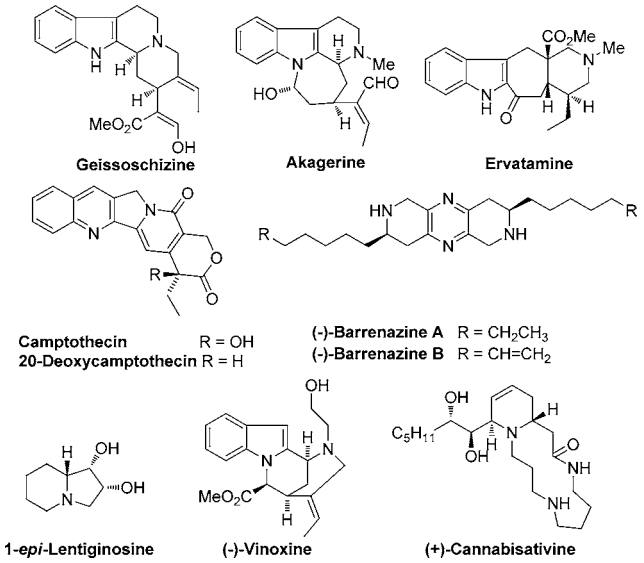
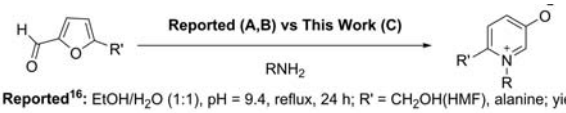


Figure 2. Derived natural products using pyridinium salts.[11]

of the biofuel dimethylfuran and other important commodities.[13]

In line with our ongoing research on the preparation of HMF[14] and transformation of furfural and HMF to useful building blocks,[15] in this work we present a novel strategy for the implementation of a new and competitive platform for the production of *N*-alkyl-5-hydroxy-2-(hydroxymethyl)pyridinium (HPyr)[16] from HMF. Optimization of the synthetic pathway leads to the establishment of efficient reaction conditions and purification methods as the key transformation from HMF to HPyr using various alkyl amines and alkyl diamines to promote the exclusive formation of mono-*N*-alkylpyridinium salts (Scheme 1C). Some HPyr derived from amino acids were

Scheme 1. Overview of Reported[16,17] *vs* This Work Synthetic Routes (A,B *vs* C) for the Synthesis of 3-Hydroxypyridinium Salts



A: Reported[16]: EtOH/H_2O (1:1), pH = 9.4, reflux, 24 h; R' = CH_2OH(HMF), alanine; yield 32%.
B: Reported[17]: R' = H(furfural), step 1) aminoacid (1 equiv), MeOH, NaOH, 60 °C, 0.5 h; step 2) $NaBH_4$, 0 °C, 1 h; step 3) 3 M HCl, H_2O_2 (2 equiv), 100 °C, 0.5 h, yield 55%-quant.
C: This work: R' = CH_2OH(HMF), alkylamines, terminal diamines, EtOH/H_2O (1:1), formic acid (30 mol %), 80 °C, 48 h; up to 82%.

already reported as potential bitter inhibitors. Low yields (32% for alanine) were obtained by the reaction of an amino acid with HMF (Scheme 1A).[16] An alternative reported route involves a three-step synthesis via imine reduction followed by oxidative rearrangement with bromine.[16] Recently a more efficient three-step approach was described for furfural using $NaBH_4$ and HCl/H_2O_2 respectively for the imine reduction and oxidative rearrangement steps (Scheme 1B).[17]

With an efficient and cheap starting material, fructose, we synthesized HMF for our screening reactions using our previously reported method.[14a] We initiated our catalyst screening (30 mol %) using butylamine as the model substrate and various inorganic bases, but we found ineffective results. Using potential catalysts, such as 2,6-lutidine, DBU, HCO_2Na, urea, $Ca(OH)_2$, $N(Et)_3Br$, NaOAc, Na_2HPO_4, KOAc, MgO, $CuCl_2{\cdot}2H_2O$, HCl, $Cu(OTf)_2$, CsCl, *tert*-butylacetic acid, showed ineffective results at various temperatures (see Supporting Information, SI).

Significant yield improvement was observed using 30 mol % of NH_4Cl, NH_4OAc, and $SnCl_2$ as catalysts giving, respectively, 66%, 61%, and 48% yields at 70 °C and 68%, 71%, and 59% yields at 80 °C. After 2 days of reaction using 30 mol % of acetic acid, or phosphoric acid, the variation of temperature from 70 to 80 °C gave reduced yields of reaction from 70% to 58% and from 73% to 70% respectively. Under the same conditions, only a 2% and 4% increase was found using trifluoroacetic acid and triflic acid respectively on moving from 70 to 80 °C. When using 30 mol % of formic acid as a catalyst, the yields increased significantly from 57% to 77% with the temperature increase from 70 to 80 °C. Despite the small variations observed, interesting results were achieved using catalysts such as trifluoroacetic acid, phosphoric acid, acetic acid, formic acid, or triflic acid at different temperatures. We decided to use these catalysts for further screening to obtain optimized reaction conditions.

HMF decomposes quickly at higher temperatures with no product observation. At lower temperatures below 70 °C, the reaction proceeds slowly and does not lead to completion even after 4 days. With those acidic catalysts that provided better yields for this reaction at 70 and 80 °C, we continued our optimization by varying the reaction time. Experiments show that reaction times above 3 days generate poor reaction yields even with an increased amount of catalyst. The gummy reaction mixture at this stage after 3 days hinders the stirring process of the reaction with no increase in efficiency.

Varying the reaction conditions from 70 °C/2 days to 70 °C/3 days, we observed either a decrease in the yield (for acetic acid or phosphoric acid as a catalyst) or minimal effect (with the other acid catalysts) (Figure 3). A negligible effect from

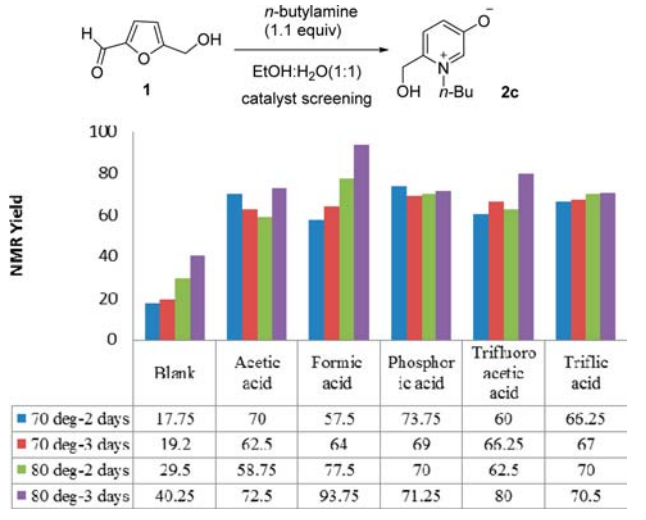


Figure 3. Screening of catalysts (30 mol %) for specific reaction time and temperature using *n*-butylamine. NMR yields using acetonitrile as internal standard.

increasing the reaction time from 2 to 3 days was also observed with phosphoric acid or triflic acid at 80 °C. However, the reaction yield improves significantly when changing the reaction time from 2 to 3 days at 80 °C using acetic acid, trifluoroacetic acid, or formic acid as a catalyst. Changing the reaction time from 2 to 3 days at 80 °C resulted in an increase in yield from 58% to 72% for acetic acid, from 62% to 80% for

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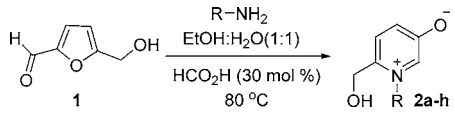
trifluoroacetic acid, and from 77% to 94% for formic acid. Thus, the optimized conditions for the reaction were set as 80 °C/3 days using 30 mol % of formic acid, with a 94% yield. We also varied the amount of catalyst, and the results show that 10 and 20 mol % of formic acid (with *n*-butylamine) provided yields of 69% and 50% respectively, whereas any increase above 30 mol % in the catalyst did not affect the reaction.

Using the optimized reaction conditions we performed the reaction with various alkyl amines (Table 1). For most cases, the reaction completion was observed at 80 °C/2 days. However, for amines with longer alkyl chains, the reactions take place slowly, and 80 °C/3 days are needed for the reaction to complete. For example, the isolated yield using hexylamine was 34% for an incomplete reaction at 80 °C/2 days, which increased to 55% if we allow the reaction to proceed for 3 days (Table 1, entry 5). Several attempts were performed with aryl amines; however, the reaction yields were poor. In contrast, shorter alkyl amines, such as methylamine, propylamine, butylamine, or pentylamine, gave better isolated yields of ~70−80% (entries 1−4), whereas longer alkyl chain amines such as hexyl or octyl amines gave lower yields, 55% and 13%, respectively (entries 5,6). Reactions with longer alkylamines were comparatively slow showing only the presence of unreacted amines but not HMF which already led to decomposition and no improvement in yield. In a 5 g scale up reaction of HMF with methyl amine, we observed an isolated yield of 80%. In the case of octylamine, 1 equiv of formic acid was used intentionally for a longer reaction time to improve the yield (30% vs 13%, entry 6). In some cases, an excess of unreacted amines were inseparable from the final pyridinium salt.

Interestingly, the reaction with hexyl diamine exclusively formed monopyridinium salt (Table 2) even with 2 mol equiv of HMF (Table 2, entry 4). This fact expanded the substrate scope, and we were able to isolate various pyridinium salts from different alkyl diamines in good yields. Also longer chain diamines gave higher yields in comparison with simple alkyl amines. For instance, octyl amine provided only a 13% yield whereas octyldiamine under similar conditions afforded a 63% yield (Table 1, entry 6 vs Table 2, entry 6).

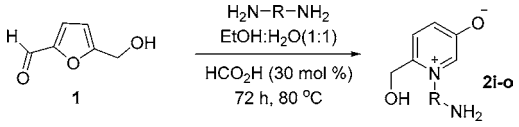
Table 1. Substrate Scope with Various Alkyl Amines[a]



entry	R	time (h)	product	yield (%)
1	methyl-	48	**2a**	78(80)[b]
2	*n*-propyl-	48	**2b**	81
3	*n*-butyl-	48	**2c**	82
4	*n*-pentyl-	48	**2d**	72
5	*n*-hexyl-	48	**2e**	34
		72		55
6	*n*-octyl-	72	**2f**	13
		72[c]		30
7	allyl-	48	**2g**	77
8	3-methoxypropyl-	48	**2h**	62

[a]Reaction conditions: To HMF (100 mg, 0.8 mmol) in EtOH/H_2O (1:1, 10 mL), 1.1 equiv of the respective amine and HCO_2H (30 mol %) were added and the mixture was heated in a closed high pressure vessel at 80 °C for 48 or 72 h. [b]5 g of HMF (40 mmol) were used. [c]1 equiv of HCO_2H was used.

Table 2. Substrate Scope with Various Diamines[a]

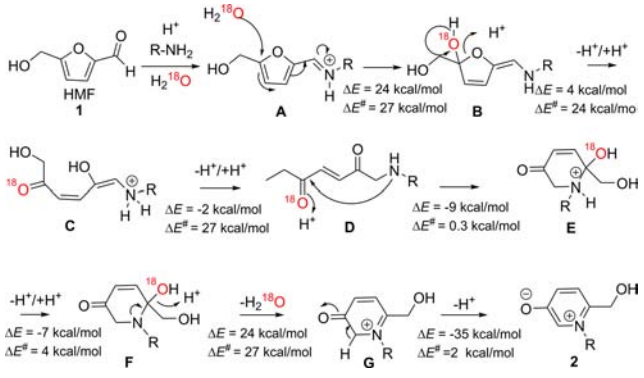


entry	R		product	yield
1	$-(CH_2)_3-$		**2i**	61
2	$-(CH_2)_4-$		**2j**	72
3	$-(CH_2)_5-$		**2k**	80
4	$-(CH_2)_6-$	HMF/diamine 1:1[b]	**2l**	70
		HMF/diamine 2:1[c]		74
5	$-(CH_2)_7-$		**2m**	69
6	$-(CH_2)_8-$		**2n**	63
7	$-(CH_2)_{12}-$		**2o**	59

[a]Reaction conditions: Same reaction conditions as in Table 1 (72 h). [b]1:1 molar ratio of HMF/diamine was used. [c]2:1 molar ratio of HMF/diamine was used.

With the purpose of disclosing the involved mechanism, an isotope water experiment using 99% $H_2{}^{18}O$ was performed. In order to minimize the amount of used $H_2{}^{18}O$ some experiments were conducted using H_2O in variable H_2O/EtOH ratios using *n*-butylamine as the model substrate, allowing the weighed quantity of H_2O/EtOH (0.167g: 0.322g) to be identified as the minimum quantity of water to be used (see SI). Under those conditions, by replacing H_2O by $H_2{}^{18}O$, the observed HRMS of the product **2c** revealed that there is no incorporation of 18-labeled isotopic oxygen (see SI) which is consistent with the mechanistic approach for the formation of pyridinium betaine via intermediate **D** (Scheme 2). In principle, HMF **1** forms an imine with a respective amine and water attacks at the C5 carbon resulting in the ring opening of furan to form intermediate **D**. The obtained intermediate undergoes an intramolecular nucleophilic attack of nitrogen onto the C2-carbonyl group leading to ring closure to form six-membered ring **E**, which follows a dehydration reaction to give the final pyridinium betaine compound **2**.

Scheme 2. Proposed Plausible Reaction Mechanism and Selected DFT Results (See Details in SI)



DFT calculations using methylamine as the substrate are also consistent with this proposed reaction pathway (see details in SI). Two explicit water molecules (solvent) were considered in the computational model, in order to have a reasonable description for the solvent assistance on the various proton

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transfer steps along the mechanism. The complete energy profile obtained for the reaction is represented in Figures S131 and S132 (see SI). The highest observed barriers are for **A**/**B**, **B**/**C**, **C**/**D**, and **F**/**G** intermediate steps. In addition, the **A**/**B** and **F**/**G** steps are clearly endoenergetic while **G**/**2** is a highly exoenergetic step derived from the aromaticity gain associated with the formation of the pyridinium cation.

The larger values obtained for the individual barriers along the path are 27 kcal/mol, and the highest point in the profile (TSC′D) is 33 kcal/mol above the initial reactants which is in reasonable agreement with the experimental conditions of the reaction (2 days at 80 °C). Nevertheless, it is important to notice that the accuracy of the energy values is somewhat limited by the modesty of the model used in the calculations, with only two explicit water molecules in a mechanism where solvent plays a decisive part. The mechanism proposed in Scheme 2 was reproduced by the DFT calculations. In the path obtained water plays a crucial role, not only as a proton carrier, assisting all the proton transfer steps, but also as an active participant in the reaction, being added to the furan ring of the initial iminium salt and lost in the final steps that lead to the pyridinium product **2**.

In conclusion, an efficient organocatalyzed transformation under mild conditions of the bioplatform HMF to *N*-alkyl-5-hydroxy-2-(hydroxymethyl)pyridinium (HPyr) salts by reaction with a range of alkylamines is described. In particular, it was also proven that in the case of using terminal alkyldiamines there is an exclusive formation of mono-HPyr. In addition, no incorporation of $H_2{}^{18}O$ was observed from the reaction medium. This synthetic route opens the possibility to consider those highly functionalized pyridinium salts as useful building blocks derived from biomass.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02573.

Experimental procedures, compounds spectral data, copies of ^{1}H NMR spectra of catalyst screening, copies of ^{1}H, ^{13}C NMR and HRMS spectra for all new compounds and DFT details (PDF)

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Notes

The authors declare no competing financial interest.

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