

Catalytic Activation of Carbohydrates as Formaldehyde Equivalents for Stetter Reaction with Enones

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S Supporting Information

ABSTRACT: We disclose the first catalytic activation of carbohydrates as formaldehyde equivalents to generate acyl anions as one-carbon nucleophilic units for a Stetter reaction. The activation involves *N*-heterocyclic carbene (NHC)-catalyzed C–C bond cleavage of carbohydrates via a retro-benzoin-type process to generate the acyl anion intermediates. This Stetter reaction constitutes the first success in generating formal formaldehyde-derived acyl anions as one-carbon nucleophiles for non-self-benzoin processes. The renewable nature of carbohydrates, accessible from biomass, further highlights the practical potential of this fundamentally interesting catalytic activation.

 \mathbf{F} ormaldehyde, a basic building block in chemical synthesis, is commonly used as a one-carbon electrophile.¹ With *N*heterocyclic carbenes (NHCs) as the catalysts,^{2,3} through polarity inversion,⁴ formaldehyde can be activated to generate an acyl anion intermediate as a one-carbon nucleophile. However, due to the highly electrophilic nature of formaldehyde, its reactions *via* NHC catalysis are limited to self-benzoin-type condensations (Scheme 1a).⁵ The self-benzoin reaction is a facile process that can go to completion in ~5 min, as reported previously^{5c} and observed in our own studies. The formaldehyde-benzoin reactions lead to the formation of glycolaldehyde, 1,3-dihydroxyacetone (DHA), and other longer chain





carbohydrates or their isomers (Scheme 1a).⁵ These benzointype reactions can be made reversible.^{5a,6} However, the reversibly generated acyl anion intermediate preferably recombines with formaldehyde present in the same reaction mixture. The intrinsically high electrophilicity of formaldehyde has made trapping of the formaldehyde-derived acyl anion with other electrophiles very challenging. Accordingly, the use of formaldehyde as a one-carbon nucleophile in processes other than the self-benzoin-type reactions has remained elusive over the years.

Herein, we report the first NHC-catalyzed activation of biomass-based carbohydrates as formal formaldehyde equivalents to generate acyl anion intermediates as one-carbon nucleophiles that undergo Stetter-type^{6a,c,e,7} Michael additions to enones (Scheme 1b).

We envisioned that, by minimizing the presence of free formaldehyde and using more enforced conditions, the reactions of one-carbon acyl anion intermediates with other electrophiles might become feasible. To minimize the presence of free formaldehyde, we first hypothesized using formaldehyde selfbenzoin adducts (such as 1b-d, Scheme 1a) to generate onecarbon acyl anion intermediates through an NHC-catalyzed retro-benzoin (retro-formose) process.

To test our hypothesis, we first used DHA (1d, a formaldehyde self-benzoin product^{sb-d}) as a one-carbon acyl anion precursor and chalcone 2a as a trapping electrophile (Scheme 2). With the





commercially available thiazolium **A** as an NHC precatalyst and K_2CO_3 as a base in CH₃CN at 80 or 100 °C under conventional oil bath or microwave⁸ heating (in a sealed tube), no detectable formation of Stetter product **3a** was observed (Scheme 2). Instead, substrates **1d** and **2a** could be recovered. We then eventually found that by using a more enforced condition under

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microwave heating at 130 °C, the desired Stetter product **3a** could be obtained in 45% isolated yield (Scheme 2). Under these conditions, the formation of the Stetter product is not reversible.

Encouraged by the initial success with DHA (1d, a triose), we quickly moved to investigate biomass-based carbohydrates (such as C6-sugars) as one-carbon acyl anion precursors. As an important note, biomass (as renewable feedstock for fuels and chemicals) holds great potential for future industries.⁹ For example, the conversion of carbohydrates (the largest fraction of biomass) to fuels or chemicals (such as hydrogen, liquid alkanes, functional furans, etc.) has received increasing attention, as demonstrated by Dumesic and others.^{9,10} Here we first chose glucose (1e), an abundant carbohydrate, to react with chalcone **2a** for further condition optimization. The commercially available glucose starting material contained ~94% α -anomer and ~6% β -anomer, as indicated by ¹H NMR analysis. The two anomers could readily isomerize to each other under the reaction conditions. As briefed in Table 1, CH₃CN was identified as a

Table 1. Hexose Carbohydrate as One-Carbon Nucleophile:Condition Optimization



^{*a*}1.0 equiv of 1e (94% α -anomer and 6% β -anomer) was used unless otherwise specified. ^{*b*}Yield was determined *via* ¹H NMR analysis of crude reaction mixture with 1,3,5-trimethoxy benzene as the internal standard (see SI); for entry 3, 79% is isolated yield.

suitable solvent and K_2CO_3 was an effective base. The commercially available thiazolium precatalyst **A** could mediate the reaction to give the Stetter product **3a** with 58% yield in 10 min at 130 °C under microwave heating (Table 1, entry 1). A smaller thiazolium precatalyst **B** could also catalyze the Stetter reaction with a slightly better yield (61%); the yield was further improved to 80% yield when the reaction time was prolonged to 30 min (entries 2, 3). Imidazolium- and triazolium-based catalysts (such as **C** and **D**) were not effective for this reaction (entries 4, 5). When the reaction was carried out using conventional oil bath heating under otherwise identical conditions, an ~10% yield of the Stetter product **3a** was observed (entry 6). With a longer reaction time (5 h) under oil bath heating, **3a** was obtained in 45% yield (entry 7). We then found that as low as 0.2 equiv of glucose (**1e**) (relative to

chalcone 2a) was sufficient to give product 3a with an acceptable 53% yield. This demonstrated that 1 equiv of a C6-sugar could generate multiple equivalents of a one-carbon acyl anion intermediate (entry 9).

Key steps for the activation of C6-sugar (1e) to generate a onecarbon acyl anion intermediate are shown in Scheme 3. The

Scheme 3. Postulated Pathway for Carbohydrate Activation



hexose is in equilibration between its cyclic acetal (1e) and acyclic aldehyde (1e') forms. The initial step involves a nucleophilic addition of an NHC catalyst to the aldehyde functional group of hexose 1e' to give a thiazolium-bounded intermediate I. Proton transfer of I leads to intermediate II that is amenable to undergo a retro-benzoin process with a C-C bond cleavage of the carbohydrate to form acyl anion intermediate III. The acyl anion III functions as a one-carbon nucleophile to undergo a Stetter reaction with chalcone 2a to afford product 3a and regenerate the NHC catalyst. During the key carbon–carbon bond breaking step (II to III), a one-carbon degraded carbohydrate (e.g., C5 sugar 4a) is released. This sugar (4a) then undergoes a similar catalytic process to generate acyl anion intermediate III and produces a smaller carbohydrate (C4 sugar) that can further undergo iterative catalytic cycles to generate III. GC-MS analysis confirmed the formation of C5- and C3-sugars in the reaction mixture (see Supporting Information (SI) for details). The C2-sugar was not detected. The presence of the C4sugar intermediate was not confirmed at this moment due to the challenging GC-MS analysis of the complex reaction mixture. Additional mechanistic studies and the use of these shorter-chain sugars for other syntheses are in progress.

To further demonstrate the generality of this strategy with carbohydrates as precursors for one-carbon nucleophiles, we studied a set of commercially available natural saccharides (Chart 1). The three C6-sugars (1e-g) examined were all effective in giving 57–81% yields of Stetter product 3a after 10 min. Generally, higher yields were achieved when the reaction was carried out for 30 min. Further extension of the reaction time (beyond 30 min) showed no apparent improvement in the yields likely due to deactivations of the NHC catalyst and unidentified side reactions of chalcones. Several C5-sugars (1h-j) were then examined. It is interesting to note that most of the C5-sugars (1h-j) were more effective than the C6-sugars (1e-g) studied. Good to excellent yields (68-83%) of the Stetter product 3a

Chart 1. Examples of Carbohydrates^a



^aYields were determined via ¹H NMR analysis unless otherwise noted.

were obtained after 10 min. For example, the use of arabinose (1h), a C5-sugar, led to nearly complete conversion of the chalcone substrate 2a. The reaction was very clean, and the product 3a could be obtained with high purity after a simple workup. The less-than-perfect yield (81% isolated yield of 3a using sugar 1h) was mainly due to unidentified side reactions of the chalcone. As little as 0.25 equiv of 1h (relative to chalcone 2a) could be used to give 3a with 55% yield. Remarkably, both disaccharides (1k, 1l) and a polysaccharide (cellulose 1m) could be used as well, albeit with diminished yields (7-11%) under current conditions. Apparently, extensive studies are still needed to develop more practically useful protocols especially for cellulose and other polysaccharides. The anomerically blocked nonreducing sugar sucrose (11) was previously reported to undergo degradation to form fragments such as C3-sugars (e.g., hydroxyacetone 1d^{11b}) under basic conditions.¹¹ These fragments could behave as HCHO equivalents under our catalytic conditions as shown in Scheme 2. Additional studies to further understand the mechanisms and improve the reaction efficiencies for such saccharides are in progress.

Among the carbohydrates studied here, the C5-sugar arabinose (1h) performed slightly better than the others to give clean reactions with good yields (83%) within 10 min. Therefore, we used arabinose 1h as the one-carbon acyl anion precursor to evaluate the scope of the enone electrophiles. As briefed in Chart 2, the reactions were facile (completed in 10 min) and tolerated chalcones with different substitution patterns. The desired Stetter products were obtained in 57–86% isolated yields (3a–o). Enone with a β -alkyl substituent could be used as well, albeit with a relatively low yield (3p, 43%). Fully aliphatic enones, such as 3-octen-2-one and cyclohexenone, were also tested. Cyclohexenone led to no detectable formation of the Stetter product; 3-octen-2-one could give the Stetter product but with less than 5% yield.

The Stetter products (β -formyl ketones) are useful building blocks, and their preparation using reported methods typically requires multiple steps.¹² For instance, the β -formyl ketones could be easily transformed to furans and pyrroles^{12d,13} (Chart 3) that can be used as basic synthons or bioactive reagents.¹⁴ Here

Chart 2. Examples of Enones^a



^{*a*}Conditions same as those for Chart 1 (1h); yields were isolated yields after SiO₂ column chromatography.

Chart 3. Synthetic Transformation of Stetter Adduct^a



^aIsolated yields based on chalcone **2a** (overall yields of the one-pot two-step operation).

the synthesis of furans/pyrroles could also be realized in an efficient one-pot procedure starting from carbohydrates and chalcones as the raw materials (Chart 3).

In summary, we have developed the first NHC-catalyzed activation of carbohydrates to generate acyl anion intermediates as one-carbon nucleophiles for Stetter reactions. The acyl anion generation involves a retro-benzoin-type process and catalytic C–C bond breaking of carbohydrates. Carbohydrates are renewable and derived from biomass, and the Stetter products (β -formyl ketones) are useful synthetic building blocks that cannot be easily prepared using other methods. Since the carbohydrate activation cycles involve multiple intermediates, we expect that other interesting transformations can be developed by intercepting some of the catalytic steps. The search for other catalytic activation modes of carbohydrates and subsequent transformations is currently being pursued in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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