



HAL
open science

Single-step sustainable production of hydroxyl-functionalized 2-imidazolines from carbohydrates

Yu Feng, Christophe Darcel, Cedric Fischmeister

► **To cite this version:**

Yu Feng, Christophe Darcel, Cedric Fischmeister. Single-step sustainable production of hydroxyl-functionalized 2-imidazolines from carbohydrates. *ChemSusChem*, 2022, 15 (3), pp.e202102361. 10.1002/cssc.202102361 . hal-03514260

HAL Id: hal-03514260

<https://hal.science/hal-03514260>

Submitted on 21 Mar 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Single-step sustainable production of hydroxyl-functionalized 2-imidazolines from carbohydrates

Feng Yu,^{*[a][b]} Christophe Darcel,^[a] and Cédric Fischmeister^{*[a]}

[a] Dr. F. Yu, Prof. Dr. C. Darcel, Dr. C. Fischmeister
CNRS, ISCR (Institut des Sciences Chimiques de Rennes)
Univ. Rennes
UMR 6226, F-35000, Rennes (France)
Email: fengyu16@zju.edu.cn or fengyu16@gmail.com
Cedric.fischmeister@univ-rennes1.fr

[b] Dr. F. Yu
Present address : Department of Chemistry, Zhejiang University
Hangzhou 310028, China

Supporting information for this article is given via a link at the end of the document.

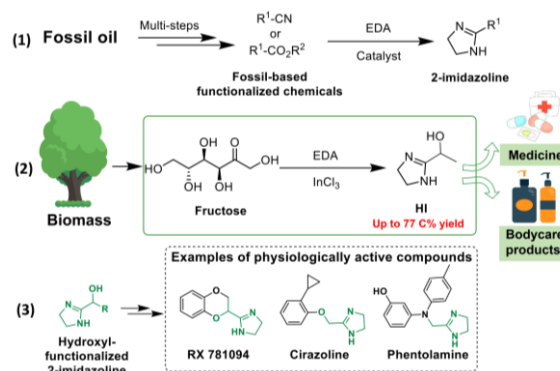
Abstract: Manufacturing valuable *N*-containing chemicals from biomass is highly desirable yet challenging. Herein, we report a novel strategy for efficient production of 2-(1-hydroxyethyl)-imidazoline (HI), a high-value and versatile building block for synthesizing a myriad of bioactive targets, directly from carbohydrates under mild reaction conditions. With this strategy, bio-based HI was produced from fructose in one step with as high as 77 C% isolated yield in the presence of ethylenediamine (EDA) and InCl_3 at 130 °C. The synergistic functions of EDA and InCl_3 were identified for the transformation, wherein EDA promoted the scission of C–C bond of fructose backbone via Retro-Aldol (R-A) reaction and rapidly trapped in-situ formed reactive carbonyl-containing C_3 intermediate for HI formation to avoid undesired side reaction, and InCl_3 facilitated the formation of this C_3 intermediate and final 1,2-hydrid shift step.

From environmental and sustainable points of view, it is highly desirable to produce valuable *N*-containing platform chemicals from renewable biomass resources.^[1,2] Currently, direct transformation of biomass, such as carbohydrates, into *N*-containing chemicals seems a formidable task due to the fact that complicated reaction pathways can be involved to introduce additional nitrogen atoms into the pristine carbon-oxygen based structures. Despite the particularly important role of *N*-containing chemicals played in agricultural, pharmaceutical and cosmetic industries,^[3] to date only very limited types of *N*-containing chemicals, such as acrylonitrile,^[4] short diamines,^[5,6] amino acids,^[7] pyrrole^[8] and 2-methyl pyrazine,^[9] have been exploited from biomass components. However, production of *N*-containing chemicals, especially bearing heterocyclic moiety, usually suffer from stringent reaction conditions and low product selectivity. For instance, catalytic conversion of sugars in the presence of ammonia solution at 180 °C afforded 2-methyl pyrazine, as the main product, in around 21 C%.^[9] These facts highlight some of the significant challenges that are encountered while attempting the synthesis of value-added heterocyclic chemicals directly from biomass resources.

2-imidazoline is a class of important heterocyclic compounds due to its potent biological activity and surfactant property.^[10,11] Among various 2-imidazolines, hydroxyl-functionalized 2-imidazoline is of particular appeal, as the extra hydroxy functional group renders it particularly useful for the synthesis of a plenty of physiologically active compounds, such as RX 781094, cirazoline and

phenolamine as adrenergic antagonists (Scheme 1.3).^[12,13] The conventional manufacture of 2-imidazoline mainly relies on the condensation of EDA with costly pre-functionalized fossil-based chemicals, such as nitriles and esters, which usually involve several synthetic steps from fossil fuel (Scheme 1.1).^[14] Developing novel sustainable synthetic routes to 2-imidazoline from renewable biomass resources such as carbohydrates, in a straightforward and efficient way, is highly desirable.

In carbohydrate chemistry, the R-A reaction is known to be favoured at high temperatures and the cleavage of C–C bond usually necessitate a temperature above 160 °C.^[15,16] This high-temperature prerequisite for sugar R-A reaction can be circumvented by introducing a primary or secondary amine, as recently disclosed by Sels *et al.*^[5,6] The amine was found to function in a similar manner as the catalysis process of nature-evolved aldolases to promote the C–C bond scission via R-A reaction, therefore resulting in a low energy requirement (~125 °C).^[5,17] Transition metal salts inherited with Lewis acid property are well recognized catalysts for converting carbohydrates to lactic acid (LA) as well as synthesizing heterocyclic compounds via facilitating hydride shift.^[18–20] In carbohydrates-to-LA transformation, pyruvaldehyde (PA) is an important intermediate which is highly reactive under high-temperature reaction conditions due to the existence of two carbonyl groups. The side reactions triggered by carbonyl-containing compounds mainly account for the low carbon balance of the carbohydrate reaction



Scheme 1. (1) Conventional synthesis of 2-imidazoline, (2) the proposed one-step conversion of fructose to 2-(1-hydroxyethyl)-imidazoline (HI), (3) examples of physiologically active compounds from hydroxy 2-imidazolines.

COMMUNICATION

by forming cumbersome by-products, such as humin. We envisage that by using EDA and metal salt not only the fragmentation process for sugars can be accelerated, but also the highly reactive PA in the reaction media can be trapped and reacted, giving rise to the one-step formation of stable *N*-containing heterocyclic chemicals.

Herein, we propose a novel approach for direct conversion of carbohydrates to HI catalyzed by metal chloride salts in the presence of EDA. The transformation can be achieved through a one-pot reaction involving the fragmentation of sugars into triose-based fragments via EDA promoted R-A cleavage and a subsequent synthesis of HI product catalyzed by a metal chloride salt. Based on this strategy, fructose and even polysaccharide inulin can be efficiently converted to HI under quite mild reaction conditions (110–150 °C).

Our study began with screening a wide variety of salts, mainly metal chlorides, for the aminolysis of fructose with EDA in air at 140 °C. HI, derived from C₃ fragment, was obtained as the main product in these reactions after 3 h, as shown in Figure 1. The product yield, given in C%, was determined by gas chromatography and represented the fraction of carbon originating from the sugar feedstock that was found in the product. The addition of metal salt generally improved the catalytic performance for HI production except using NiCl₂, CoCl₂ and alkali metals (LiCl and NaCl), which gave similar yields to the blank test (8%) without metal salt. Among all metal salts tested, InCl₃ exhibited the highest catalytic performance, affording 2-imidazoline product in 65% yield. Other metal salts, including AlCl₃, CrCl₃, FeCl₃, Fe(OTf)₃, YCl₃, ZrCl₄, CeCl₃, NdCl₃·6H₂O and EuCl₃·6H₂O also afforded decent product yields, showing in the range of 48–62%. The significant difference in catalytic performance of Fe(III) salts (~50% from FeCl₃ and Fe(OTf)₃) and Fe(II) salts (~20% from FeCl₂) revealed that the Lewis acidity property of metal salts possibly played a crucial role in this catalytic transformation. Considering the higher catalytic efficiency of InCl₃, this catalyst was selected for further investigations.

The influence of reaction temperature, loading of InCl₃, H₂O content and reaction atmosphere were further investigated. The results indicated that the temperature of 130 °C (Table S1), 7.5 mol% of InCl₃ (Figure S3), and inert reaction atmosphere (Table S2, entries 1 and 2) were the best choices for efficient conversion of fructose to HI. An appropriate amount of H₂O (less than 16.7 mmol) in the catalytic system was found to be necessary for achieving high catalytic reaction efficiency since both overmuch and deficient H₂O led to a substantial drop in product yield (Table S2, entries 2–9). This H₂O effect may be realized via balancing the iminization and hydrolysis steps in the cascade reactions.

To gain insights into the reaction pathways, the conversion of C₃ fragments, including glyceraldehyde (GA), dihydroxyacetone (DHA), PA and LA, which are well-known compounds arising from fructose fragmentation, was investigated at 130 °C under argon atmosphere (Table 1). Without InCl₃, conversions of GA and DHA with EDA gave only 13% and 11% yields of HI respectively, much lower than 52% obtained from PA (Table 1, entries 3, 6 and 9). On the contrary, good yields (≥ 80%) were achieved for the conversion of all three C₃ fragments in the presence of InCl₃ (Table 1, entries 1, 4 and 7), although a markedly faster reaction rate for HI formation was observed in the case of PA. No HI product could be obtained from LA even employing InCl₃ (Table 1, entry 10). These results demonstrate that GA, DHA and PA

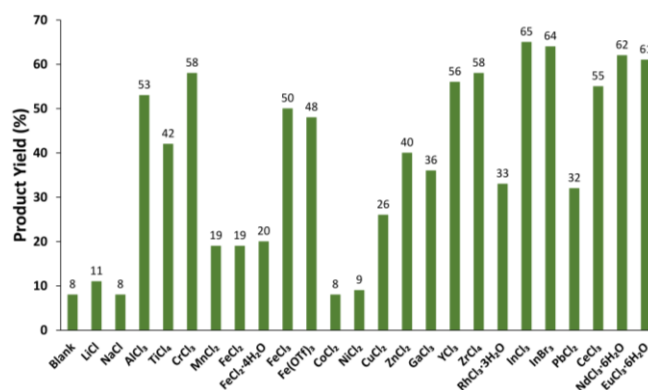


Figure 1. Catalytic performance of metal salts for the transformation of fructose to HI. Reaction conditions: fructose (180 mg, 1 mmol), EDA (1.2 g, 20 mmol), metal salt (5 mol%), 140 °C, 3 h, in air. Yields determined by GC using *n*-hexadecane as an internal standard.

Table 1. Conversion of C₃-fragments into HI^[a]

Entry	Substrate	Cat.	Time (h)	Yield (%) ^[b]
1	GA	InCl ₃	4	82
2	GA	InCl ₃	1	6
3	GA	-	4	13
4	DHA	InCl ₃	4	80
5	DHA	InCl ₃	1	5
6	DHA	-	4	11
7	PA	InCl ₃	4	85
8	PA	InCl ₃	1	40
9	PA	-	4	52
10	LA	InCl ₃	4	–

[a] substrate (0.67 mmol), InCl₃ (4 mol%), EDA (10 mmol), H₂O (5.6 mmol), 130 °C, Ar. [b] yields based on GC calculation using *n*-hexadecane as an internal standard.

could be involved in the catalytic aminolysis of fructose and InCl₃ plays a key role in the transformation of these C₃-based intermediates into HI. Among these three C₃ intermediates, PA can be most readily converted to HI. Notably, the similar yields from fructose (8%, Figure 1) and trioses (~12% from DHA and GA, Table 1, entries 3 and 6) in the absence of InCl₃ reveal the facilitating function of EDA to R-A fructose fragmentation. Altogether, these results demonstrate the crucial role of InCl₃ for the transformation of GA and DHA into PA and to a lesser extent for the transformation of PA into HI. The contribution of InCl₃ in the R-A reaction should also not be ruled out.

The monitoring of the reaction progress with time by ¹³C NMR is presented in Figure 2. The spectrum of fructose exhibits typical NMR peaks between 60 and 105 ppm. Peaks at 104.4, 101.5 and 98.1 are attributed to C-2 (anomeric carbon) of α -fructofuranose, β -fructofuranose and β -fructopyranose respectively as reported.^[21] Upon mixing fructose with EDA (t = 0 min), high field chemical shifts at 93.5–98.4 ppm for C-2 of all forms of fructose were observed, indicating the complete formation of hemiaminal,^[22] which was also corroborated by the appearance of multiple new peaks around 42.7 ppm, attributed to EDA moiety of the formed hemiaminal.

The spectrum recorded after 1 h at 130 °C showed new intensive peaks at 18.8, 39.9, 40.2, 41.7, 49.1, 57.2, 177.8 ppm, which were ascribed to the iminized 2-imidazolidine intermediate (**IM-4**) potentially generated from the conjugated imine intermediate (**IM-**

COMMUNICATION

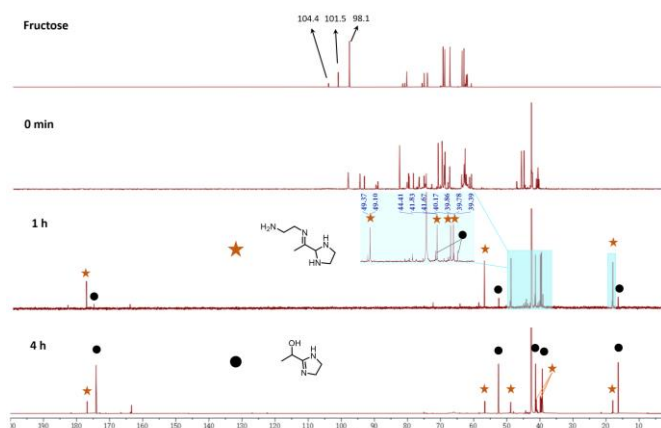


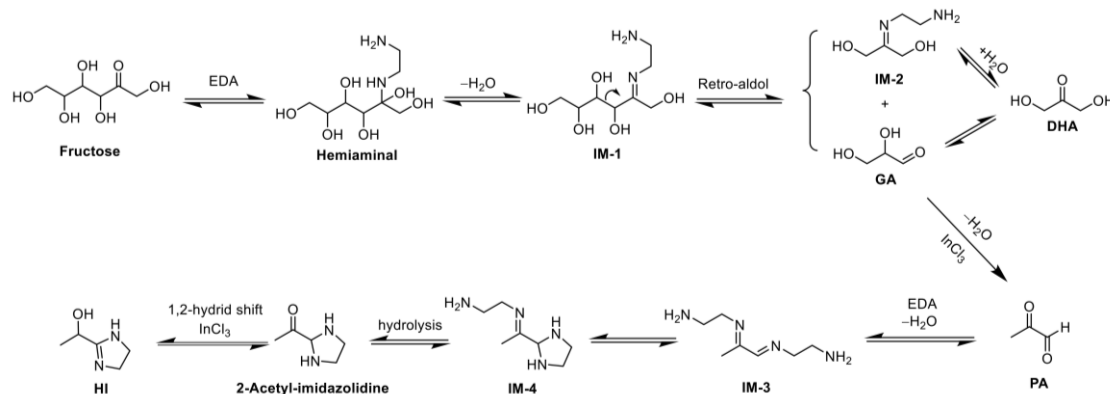
Figure 2. ^{13}C NMR spectra of fructose and the reaction mixture at different times. Reaction conditions: fructose (180 mg, 1 mmol), EDA (20 mmol), InCl_3 (7.5 mol%), 130 °C, under Ar.

3) via cyclization during the catalytic process (Scheme 2). This type of cyclization can easily take place in the reaction of aldehyde with EDA for 2-imidazoline formation according to previous reports.^[23,24] The detection of intermediate with m/z of 157 (Figure S6-3) in the reaction mixture by LC-MS further corroborated the formation of **IM-4**. In addition, characteristic peaks, including at 16.6, 39.3, 41.8, 52.7, 175.5 ppm, of HI were detected. Other small peaks appeared in the 160–190 ppm region, likely arising from various ketimine, aldimine or carbonyl (> 180 ppm) compounds involved in the overall process. With further increase of the reaction time, the product peaks evidently grew at the expense of **IM-4** consumption, being dominant in the spectrum after 4 h. It should be noted that some characteristic peaks of **IM-4** were still present even prolonging the reaction time to 24 h, implying that the formation of nitrogenous oligomers or polymers containing **IM-4** structure units, may occur because of Maillard (Browning) side reaction,^[25,26] which was supported by the colour change of the reaction mixture from colourless to dark brown.

Based on the obtained results, a plausible reaction pathway for the catalytic conversion of fructose with EDA into HI is proposed in Scheme 2. The reaction starts with a nucleophilic attack of the NH_2 group of EDA on the carbonyl function of fructose resulting in the formation of a hemiaminal intermediate. Imine species **IM-1** is then generated from the hemiaminal via dehydration and undergoes R-A fragmentation mainly facilitated by EDA to result in the cleavage of $\alpha\text{C}-\beta\text{C}$, giving rise to the two C_3 fragments, **IM-2** and **GA**. The generation of **IM-1** and **IM-2** is supported by LC-

MS analysis (Figure S6-1 and 2). Conversion of **IM-2** into GA is then achieved through equilibrium with DHA and GA is dehydrated into PA which in turn evolves to the bis-imine intermediate **IM-3** due to the large excess of EDA. 2-imidazolidine **IM-4**, readily formed from **IM-3** via cyclization, can be eventually converted into HI via a hydrolysis into 2-acetyl-imidazolidine and a subsequent InCl_3 -catalyzed 1,2-hydrid shift reaction.^[27,28] The **IM-4** hydrolysis process is in line with the above-mentioned beneficial H_2O effect in fructose-to-HI transformation (Table S2).


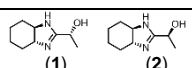
The application scope of this catalytic aminolysis process was further extended to other feedstocks, which include glucose, sucrose and inulin, representing typical monosaccharide, disaccharide and polysaccharide, respectively (Table 2). The catalytic conversion of glucose in the presence of EDA and 7.5 mol% InCl_3 at 130 °C gave 24% yield of HI after 13 h (Table 2, entry 5). Even lower product yields were obtained from sucrose (13%), a disaccharide composed of glucose and fructose, and inulin (18%), a polysaccharide consisting of fructose. The good tolerability of the glycosidic bonds to hydrolysis into monosaccharides in the weak basic medium possibly accounts for these more modest results.^[29] Indeed, when a two-step reaction strategy, comprising fructose production from inulin hydrolysis catalyzed by InCl_3 in aqueous medium and subsequent aminolysis of generated fructose to the desired HI product in the presence of EDA, was employed for one-pot conversion of inulin, HI yield can be achieved up to 53% (Table 2, entry 8). Besides the scope extension of carbohydrate feedstocks, varied 1,2-diamines can be also utilized to synthesize the corresponding hydroxyl-functionalized heterocyclic product. Taking *trans*-1,2-diaminocyclohexane as the example, the catalytic conversion of fructose with *trans*-1,2-diaminocyclohexane and 17% water in presence of InCl_3 enabled the synthesis of 2-(1-hydroxyethyl)-hexahydro-benzimidazole (HHB) with two diastereomers **1** and **2** in a ratio of 1:1.3 and in a satisfactory total isolated yield of 66%. The typical catalytic conversion of fructose under the optimized reaction conditions provided HI in 74% GC yield (Table 2, entry 1), which is comparable to the obtained 77% isolated yield (Table 2, entry 2), and 75% yield based on ^{13}C NMR quantification (Figure S4). A scale-up reaction with fructose loading of 5 g gave a comparable yield of 73% after 4 h (Table 2, entry 3). In addition, after removing the HI product and the remaining EDA by distillation under vacuum, the resultant dark brown polymeric residue containing InCl_3 catalyst (see Figure S5) was reused for the new batch of fructose conversion and afforded HI in a yield of



Scheme 2. Proposed reaction pathway for the conversion of fructose into HI in the presence of InCl_3 and EDA.

COMMUNICATION

Table 2. Catalytic conversion of carbohydrates into heterocyclic compounds in the presence of InCl₃ and 1,2-diamine.

Entry	Substrate	Time (h)	Product	Yield(%) ^[a]
1	Fructose	4		74
2	Fructose	4		77 ^[b]
3 ^[c]	Fructose	4		73
4 ^[d]	Fructose	4		75
5	Glucose	13		24
6	Sucrose	24		13
7	Inulin	13		18
8 ^[e]	Inulin	5+4		53
9	Fructose	4		66 ^[b]

Reaction conditions: substrate (1 mmol, based on monosaccharide unit), InCl₃ (0.075 mmol), EDA (20 mmol), H₂O (11 mmol), at 130 °C, under Ar. [a] GC yield using *n*-hexadecane as the internal standard unless otherwise stated. [b] Isolated yield by column chromatography. [c] A scale-up test with 5 g of fructose. [d] The reaction carried out with recycled InCl₃ catalyst. [e] The reaction was carried out via a two-step strategy (SI).

75%, identical to the fresh one, indicating a full catalytic activity of the recycled InCl₃ and implying this one-pot strategy could be served as a feasible way for sustainable synthesis of HI from carbohydrate feedstocks. The environmental factor (E-factor),^[30] a green chemistry metric, of this catalytic transformation was evaluated to be 2 when regarding both added and produced water as waste and considering the recyclability of the excess EDA (see SI), showing its superiority to the traditional synthetic processes (5–50) for fine chemicals.

In conclusion, a novel catalytic process for efficient production of bio-based HI directly from carbohydrates is presented. Up to 77% isolated yield of HI was obtained from fructose in the presence of ethylenediamine and a catalytic amount of InCl₃. For this transformation, a plausible catalytic reaction pathway via an iminized 2-imidazolidine intermediate (IM-4) was proposed and the synergistic effect of EDA and InCl₃ was identified. Moreover, this strategy is applicable to other carbohydrates, even including polysaccharide inulin, and other 1,2-diamines for corresponding heterocyclic products. It therefore represents a promising strategy for sustainable synthesis of valuable heterocyclic chemicals from biomass resources via a simple way.

Acknowledgements

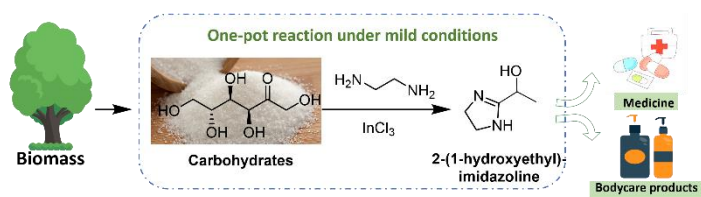
The authors thank the Centre National de la Recherche Scientifique (CNRS), The International Consortium on Ecoconception and Renewable Resources (FR CNRS 3707 INCREASE) and Université de Rennes 1 for financial support.

Keywords: biomass valorization • fructose • 2-(1-hydroxyethyl)-imidazoline • homogeneous catalysis • carbohydrates

- [1] M. Pelckmans, T. Renders, S. Van de Vyver, B. F. Sels, *Green Chem.* **2017**, *19*, 5303–5331.
 [2] X. Chen, S. Song, H. Li, G. Gözaydın, N. Yan, *Acc. Chem. Res.* **2021**, *54*, 1711–1722.

- [3] K. Nylund, P. Johansson, *Heterocyclic Compounds: Synthesis, Properties and Applications*, Nova Science Publishers, New York, **2010**.
 [4] E. M. Karp, T. R. Eaton, V. Sánchez i Nogué, V. Vorotnikov, M. J. Bidy, E. C. D. Tan, D. G. Brandner, R. M. Cywar, R. Liu, L. P. Manker, W. E. Michener, M. Gilhespy, Z. Skoufa, M. J. Watson, O. S. Fruchey, D. R. Vardon, R. T. Gil, A. D. Bratis, G. T. Beckham, *Science* **2017**, *358*, 1307–1310.
 [5] M. Pelckmans, W. Vermandel, F. Van Waes, K. Moonen, B. F. Sels, *Angew. Chem. Int. Ed.* **2017**, *56*, 14540–14544; *Angew. Chem.* **2017**, *129*, 14732–14736.
 [6] M. Pelckmans, T. Mihaylov, W. Faveere, J. Poissonnier, F. Van Waes, K. Moonen, G. B. Marin, J. W. Thybaut, K. Pierloot, B. F. Sels, *ACS Catal.* **2018**, *8*, 4201–4212.
 [7] W. Deng, Y. Wang, S. Zhang, K. M. Gupta, M. J. Hülsey, H. Asakura, L. Liu, Y. Han, E. M. Karp, G. T. Beckham, P. J. Syson, J. Jiang, T. Tanaka, Y. Wang, N. Yan, *Proc. Natl. Acad. Sci.* **2018**, *115*, 5093–5098.
 [8] S. Song, V. F. K. Yuen, L. Di, Q. Sun, K. Zhou, N. Yan, *Angew. Chem. Int. Ed.* **2020**, *59*, 19846–19850; *Angew. Chem.* **2020**, *132*, 20018–20022.
 [9] X. Chen, H. Yang, M. J. Hülsey, N. Yan, *ACS Sustain. Chem. Eng.* **2017**, *5*, 11096–11104.
 [10] R. Tyagi, V. K. Tyagi, S. K. Pandey, *J. Oleo Sci.* **2007**, *56*, 211–222.
 [11] X. Guan, Y. Hu, *Expert Opin. Ther. Pat.* **2012**, *22*, 1353–1365.
 [12] W. S. Saari, W. Halczenko, W. C. Randall, V. J. Lotti, *J. Med. Chem.* **1983**, *26*, 1769–1772.
 [13] S. S. Hong, S. A. Bavadekar, S. Il Lee, P. N. Patil, S. G. Lalchandani, D. R. Feller, D. D. Miller, *Bioorganic Med. Chem. Lett.* **2005**, *15*, 4691–4695.
 [14] R. D. Crouch, *Tetrahedron* **2009**, *65*, 2387–2397.
 [15] M. S. Holm, S. Saravanamurugan, E. Taaming, *Science* **2010**, *328*, 602–605.
 [16] M. Sasaki, K. Goto, K. Tajima, T. Adschiri, K. Arai, *Green Chem.* **2002**, *4*, 285–287.
 [17] S. Luo, P. Zhou, J. Li, J. P. Cheng, *Chem. Eur. J.* **2010**, *16*, 4457–4461.
 [18] I. Bodachivskiy, U. Kuzhiumparambil, D. B. G. Williams, *ChemSusChem* **2018**, *11*, 642–660.
 [19] C. H. Jiang, X. Lei, L. Zhen, H. J. Du, X. Wen, Q. L. Xu, H. Sun, *Beilstein J. Org. Chem.* **2014**, *10*, 2892–2896.
 [20] T. Kenichi, M. Atsushi, S. Kazuhiko, S. Shigeru, T. Hideaki, H. Yoshiaki (Nippon Shokubai CO., LTD.), WO2011125882, **2011**.
 [21] L. Qi, I. T. Horváth, *ACS Catal.* **2012**, *2*, 2247–2249.
 [22] C. I. Neglia, H. J. Cohen, A. R. Garber, P. D. Ellis, S. R. Thorpe, J. W. Baynes, *J. Biol. Chem.* **1983**, *258*, 14279–14283.
 [23] H. Fujioka, K. Murai, Y. Ohba, A. Hiramatsu, Y. Kita, *Tetrahedron Lett.* **2005**, *46*, 2197–2199.
 [24] M. Ishihara, H. Togo, *Synlett* **2006**, 227–230.
 [25] J. E. Hodge, *J. Agric. Food Chem.* **1953**, *1*, 928–943.
 [26] M. S. Feather, in *Chemical Changes In Food During Processing*, (eds.: T. Richardson, J. W. Finley) **1985**, pp. 289–303.
 [27] R. S. Assary, L. A. Curtiss, *J. Phys. Chem. A* **2011**, *115*, 8754–8760.
 [28] L. G. Zhuo, J. J. Zhang, Z. X. Yu, *J. Org. Chem.* **2012**, *77*, 8527–8540.
 [29] T. Shimanouchi, R. Mano, Y. Yoshioka, A. Fukuda, K.-M. Park, Y. Kimura, *J. Chem.* **2019**, *2019*, 1–9.
 [30] R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273–1283.

Entry for the Table of Contents



Hydroxy functionalized 2-imidazole: A new type of valuable nitrogen-containing heterocycles is exploited directly from carbohydrates *via* designing an efficient catalyst system.