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ARTICLE

Utilization of bio-based glycolaldehyde aqueous solution in organic synthesis: application to the synthesis of 2,3-dihydrofurans

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Glycolaldehyde is a biomass-derived chemical compound available from cellulose or glucose. Until now, little attention has been devoted to its use towards value-added chemicals. To explore novel transformations of glycolaldehyde, in this work, a three-component reaction of glycolaldehyde, indole and 1,3-dicarbonyl compound was developed to synthesize a class of 3-(indol-3-yl)-2,3-dihydrofurans. Using glycolaldehyde diethyl acetal as glycolaldehyde source, the reaction can be performed in organic solvents, and two catalytic systems were proved to be effective: (a) $Sc(OTf)_3$/nitromethane; and (b) $Ni(ClO_4)_2\cdot 6H_2O$/acetonitrile. However, these conditions applied to the direct use of the bio-based glycolaldehyde aqueous solution did not provide the dihydrofurans efficiently. To enable the use of the aqueous solution of glycolaldehyde, a hitherto unreported deep eutectic solvent (DES) was developed by using $FeCl_3\cdot 6H_2O$ and meglumine (*N*-methylglucamine) as precursors. The $FeCl_3\cdot 6H_2O$/meglumine DES was characterized by FTIR, TGA and DSC, and the obtained results demonstrated unambiguously the formation of a DES. This DES was found to be an efficient and a water-compatible promoting medium for the above mentioned three-component reaction. A variety of 3-(indol-3-yl)-2,3-dihydrofuranfurans were synthesized in good yields. The $FeCl_3\cdot 6H_2O$/meglumine DES system can also be recycled without significant loss of activity.

Introduction

In consideration of environmental issues and economic stress, biomass conversion has become more attractive because energy, fuels and chemicals/materials can be co-produced in the process called biorefinery. Therefore, strategies and processes devoted to the conversion of biomass have been the focus of intense research by chemists recently.[1] However, most of the biomass conversion reactions involve the formation of water. For example, pyrolysis oil derived from biomass contains 15-25 wt% water.[2] In some cases, the amount of water is so significant that it can affect notably the quality of the main product. Glycolaldehyde is one of the valuable biomass-derived platform molecules, and it can be produced by hydrolysis of cellulose or glucose followed by a selective retro-aldol condensation.[3] Nowadays, glycolaldehyde is mostly used as food browning agent.[4] It was also proved to be an intermediate in the formation of ethylene glycol or ethanolamine from glucose or cellulose.[5] Because of its unique reactivity, bio-based glycolaldehyde exhibits a great potential to be used in the synthesis of fine chemicals. However, owing to the difficulty of removing water in the bio-sourced product, it is necessary to consider using directly the aqueous solution of glycolaldehyde in the downstream value-added transformations.[6] In this context, water-compatible catalytic systems and water-compatible media, such as DES, should be the best choices.

DESs (deep eutectic solvents) are generally composed of two or three cheap and safe compounds. Intermolecular interaction of all the components lead to the formation of deep eutectic mixtures with one melting point lower than that of each individual component. Most of present widely-used DESs is choline chloride (ChCl)-based DESs.[7] It is a cheap and biodegradable quaternary ammonium salt which can be extracted from biomass. In combination with hydrogen bond donors such as carboxylic acid, polyols/sugars and amides, ChCl is liable for rapidly forming a DES. The physico-chemical properties and applications of these DESs in some areas, such as dissolution, extraction process, electrochemistry and material chemistry, have been extensively explored.[8] DESs formed by zinc chloride are also reported. These DESs are acidic, can thus be applied in organic synthesis as dual solvents/catalysts.[9] Some other metal halides were also used to

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prepare DESs. However, until now, little attention has been devoted to the rational design of task-specific DESs that allows an individualization of their catalytic uses. We focused on designing task-specific DESs for synthesis and catalysis uses.

Among possible targets are the very interesting five-membered furan and dihydrofuran rings which can be found in a fascinating array of bioactive natural products and pharmaceutical compounds.[10] Therefore, efficient synthesis of these derivatives is of high interest and consequently many procedures have been developed.[11] We have paid much attention to the ring embellishment and transformations of furan or dihydrofuran derivatives in the past decade.[12] Particularly, by combining a bifunctional aldehyde and a nucleophilic indole together, some interesting approaches to heterocyclic derivatives can be achieved.[13] Glycolaldehyde being a bifunctional nucleophilic and electrophilic species, it can therefore be possibly used as precursor for synthesizing some five-membered dihydrofurans. Considering also the bio-based origin of glycolaldehyde, if a new synthesis reaction forming a specific class of heterocycles were established, it would provide suitable routes and options for value-added transformation of biomass. Hence, we focused our effort on this topic by investigating the direct use of glycolaldehyde aqueous solution towards furans and we report herein our preliminary results obtained in this endeavor.

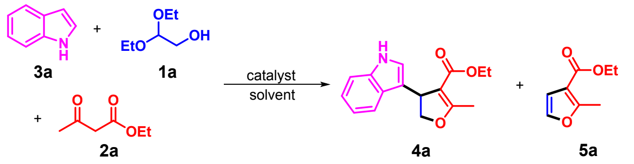
Results and discussion

Although glycolaldehyde is a commercially available compound, but it is very expensive. Considering also the fact that it is not stable under acidic conditions, we used glycolaldehyde acetal, an easily available and inexpensive reagent, as a source of glycolaldehyde. Under acidic conditions, glycolaldehyde can be released via deacetalization reaction.[14] Initially, a mixture of glycolaldehyde diethyl acetal **1a**, ethyl acetoacetate **2a** and indole **3a** was treated under the conditions tabulated in **Table 1**. Theoretically speaking, the molar ratio of **1a/2a/3a** was 1/1/1 for the synthesis of the target dihydrofuran **4a**. Taking into account that a by-product, ethyl 2-methyl-3-furancarboxylate **5a**, might be formed through a reaction of **1a** and **2a**,[15] and the molar ratio of **1a/2a/3a** was temporarily fixed at 2/2/1 with the aim of obtaining higher **4a** yields.

In the absence of catalyst, no reaction occurred after 1 h of reaction at 80 °C in acetonitrile or nitromethane (**Table 1**, entry 1). When $Sc(OTf)_3$ was used as catalyst in conjunction with using nitromethane as solvent, **3a** consumed rapidly at room temperature, and **4a** was isolated in 81% yield after 1 h of reaction (entry 2). $Al(OTf)_3$ and $Fe(OTf)_3$ were also able to catalyze this reaction, but the yields of **4a** were inferior as compared with $Sc(OTf)_3$ (entries 3 and 4). The formation of a by-product **5a** could be clearly observed in these cases, which was partially responsible for the insufficient synthesis of **4a**. When $Ni(OTf)_2$ and $Ni(ClO_4)_2{\cdot}6H_2O$ were used, only unreacted starting materials were recovered (entry 5). A strong Brønsted acid, *p*-toluenesulfonic acid (TsOH), was also examined under the identical conditions, but no product can be detected (entry 6). Then, the effect of solvent was explored. Among all the solvents screened, nitromethane clearly stood out with acetonitrile in a near second place (entries 2 and 7). The reaction proceeded sluggishly in 1,2-dichloroethane and toluene, producing **4a** only in moderate yields (entries 8 and 9). Ethanol was proven to be inappropriate for this reaction (entry 10).

Although the target dihydrofuran **4a** can be synthesized in good yield, owing to the use of nitromethane, which is a toxic and an explosive solvent,[16] the greenness of $Sc(OTf)_3$/nitromethane system is thus far from satisfactory. The significant solvent effect observed over $Sc(OTf)_3$ catalyst led us to scrutinize the catalytic activities of some other acids in different solvent systems. From the viewpoint of industrial uses, acetonitrile is much better than nitromethane although it is still toxic. This can be witnessed by the wide uses of acetonitrile in pharmaceutical synthesis.[17] We therefore paid our attention particularly to acetonitrile. It was found that, by using $Ni(ClO_4)_2{\cdot}6H_2O$ as catalyst (20 mol%), the reaction proceeded very well at 80 °C. And **4a** could be obtained in 79% yield after 6 h of reaction (entry 11). But, the formation of **5a** was unavoidable. The reaction over $Ni(OTf)_2$ catalyst proceeded also smoothly. However, perhaps due to the easy formation of **5a**, the yield of **4a** reached only 61% (entry 12). For the reaction over $Ni(ClO_4)_2{\cdot}6H_2O$ catalyst, solvent effect is also significant, which can be verified by the results obtained with toluene and ethanol, and those are inappropriate for this reaction (entries 13 to 15). At this stage of our study, two systems were identified to be suitable to implement the synthesis of **4a**: (**A**) $Sc(OTf)_3$ (5 mol%)/nitromethane, with this system, the reaction can be performed at room temperature, and finished within 1 h; and (**B**) $Ni(ClO_4)_2{\cdot}6H_2O$ (20 mol%)/acetonitrile, with this system, the reaction has been performed at 80 °C, and 6 h are needed to get a good reaction yield (optimization of the reaction parameters, such as temperature and reaction time, is given in SI, **Table S1**).

Table 1. Three-component reaction of **1a**, **2a** and **3a**.[a]



entry	catalyst and specified conditions	yield (%)[b]	
		4a	**5a**[c]
1	catalyst-free, in CH_3CN or CH_3NO_2, 80 °C, 1 h	0	0
2	$Sc(OTf)_3$ (5 mol%), CH_3NO_2, r.t., 1 h (method **A**)	81	0
3	$Al(OTf)_3$ (5 mol%), CH_3NO_2, r.t., 1 h	50	16
4	$Fe(OTf)_3$ (5 mol%), CH_3NO_2, r.t., 1 h	63	14
5	$Ni(OTf)_2$ or $Ni(ClO_4)_2{\cdot}6H_2O$ (5 mol%), CH_3NO_2, r.t., 1 h	0	0
6	PTSA (5 mol%), CH_3NO_2, r.t.,1 h	0	0
7	$Sc(OTf)_3$ (5 mol%), CH_3CN, r.t., 1 h	73	8
8	$Sc(OTf)_3$ (5 mol%), DCE, r.t., 1 h	47	14
9	$Sc(OTf)_3$ (5 mol%), Toluene, r.t., 1 h	39	17
10	$Sc(OTf)_3$ (5 mol%), EtOH, r.t., 1 h	0	0
11	$Ni(ClO_4)_2{\cdot}6H_2O$ (20 mol%), CH_3CN, 80 °C, 6 h (method	79	12

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	B)		
12	Ni(OTf)$_2$ (20 mol%), CH_3CN, 80 °C, 6 h	61	15
13	Ni(ClO$_4$)$_2$·6H$_2$O (20 mol%), DCE, 80 °C, 6 h	57	16
14	Ni(ClO$_4$)$_2$·6H$_2$O (20 mol%), Toluene, 80 °C, 6 h	13	0
15	Ni(ClO$_4$)$_2$·6H$_2$O (20 mol%), EtOH, 80 °C, 6 h	11	0

[a]: **1a** (0.4 mmol), **2a** (0.4 mmol), **3a** (0.2 mmol), solvent (1.0 mL). [b]: Isolated yield, and calculated with respect to **3a**. [c]: Isolated yield, and calculated with respect to **1a**.

The effect of catalyst amount on the model reaction was then investigated. As shown in **Figure 1**, the performance of the model reaction was influenced quite notably by the amount of Sc(OTf)$_3$ or Ni(ClO$_4$)$_2$·6H$_2$O. Increasing the concentration of these acid catalysts in general led to improvement of the reaction yield. For Sc(OTf)$_3$/nitromethane system, this tendency is quite obvious when the amount of Sc(OTf)$_3$ is lower than 2.0 mol% (**Figure 1, a**). While the yield of **4a** can be improved from 15% to 67% by increasing the loading of Sc(OTf)$_3$ catalyst from 0.5 mol% to 2.0 mol%, an increase of the scandium loading from 2.0 mol% to 5.0 mol% gained only 14% of yield increase. Taking together with the mild conditions and the short reaction time (1 h) of the method **A**, these results imply that the catalytic activity of Sc(OTf)$_3$ is quite high, and a small amount of Sc(OTf)$_3$ is sufficient enough to initiate the reaction. Indeed, when 0.5 mol% of Sc(OTf)$_3$ was used, the yield of **4a** can be improved to the same level by elongating the reaction time to 12 h (See SI, **Table S2**). This was because small reaction rate than deactivation of catalyst. In method **B**, with Ni(ClO$_4$)$_2$·6H$_2$O catalyst/acetonitrile system, 5.0 mol% of catalyst is sufficient enough to provide over 60% of yield under the standard conditions. Different from method **A**, the yield cannot be improved further by simply elongating the reaction (See SI, **Table S2**). Changing of the catalyst amount from 5.0 mol% to 20.0 mol% led to only 17% of yield increase.

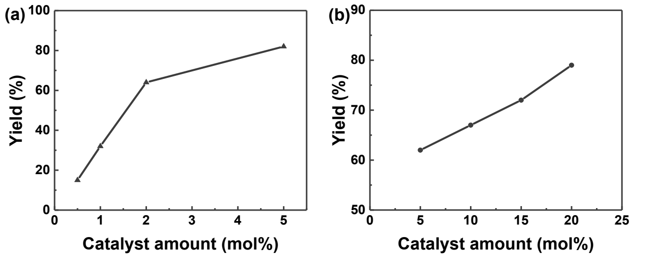

Figure 1. Effect of the catalyst amount on the model reaction. (a) Sc(OTf)$_3$/nitromethane, r.t., 1 h (method **A**). (b) Ni(ClO$_4$)$_2$·6H$_2$O/acetonitrile, 80 °C, 6 h (method **B**).

Given that bio-based glycolaldehyde is generally produced in water, and is rather difficult to obtain in an anhydrous form with a high degree of purity, a water-compatible system should be preferable for updating bio-based glycolaldehyde to value-added products. To this end, we then investigated the effect of water to methods **A** and **B** for the synthesis of **4a**. As evidenced by the results in **Figure 2**, in a reaction in 0.2 mmol scale, addition of water resulted in dramatic decrease of the reaction yield. Sc(OTf)$_3$/nitromethane seems more sensitive toward water than Ni(ClO$_4$)$_2$·6H$_2$O/acetonitrile. It is reasonable considering the fact that a small amount of water has already induced into the reaction system as the hydrate of the Ni(II) salt in method **B**. It should be mentioned that water is immiscible with nitromethane, and as a result, a biphasic system can be formed after adding some amounts of water with method **A** (the left picture in **Figure 2**). But, the reaction with method **B** is still a homogeneous system (the right picture in **Figure 2**). Whatever happens, after adding 7 mmol (0.13 g) of water into the reaction system, the yield of **4a** sharply reduced to < 20%. These results imply that methods **A** and **B** are both unable to implement the synthesis of **4a** by using an aqueous solution of bio-based glycolaldehyde as precursor. Therefore, a water-compatible catalytic system that enables the use of bio-based glycolaldehyde is still appealingly needed.

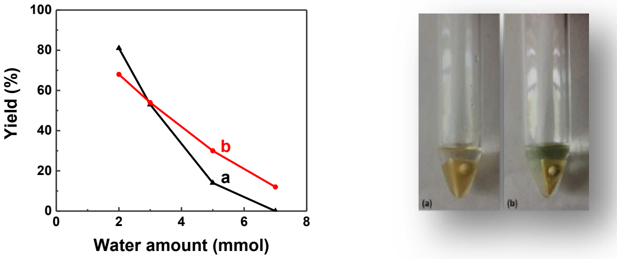

Figure 2. Effect of the water amount on the model reaction. (a) Sc(OTf)$_3$/nitromethane, r.t., 1 h (method **A**). (b) Ni(ClO$_4$)$_2$·6H$_2$O/acetonitrile, 80 °C, 6 h (method **B**).

On the other hand, DESs have gained much attention in the past decade.[18] Like ionic liquids[19], DESs are generally less-volatile and their properties can be finely tuned by changing the component structures and the ratio of different components. But they have notable advantages, such as easy preparation, low cost and good recyclability. Therefore, DESs have been widely used as eco-friendly and sustainable alternatives to the conventional organic solvents in synthetic chemistry. Some of DESs can be synthesized by using metal halides as hydrogen bond acceptors (HBAs) in conjunction with the uses of amides, carboxylic acids or polyols as hydrogen bond donors (HBDs).[20] This class of DESs are acidic, can thus be applied in organic synthesis as dual solvents/catalysts. We conjectured that acidic DESs might be suitable promoting media for aforementioned three-component reaction with high efficiency. To verify our hypothesis, a novel deep eutectic solvent (DES) was synthesized from FeCl$_3$·6H$_2$O and meglumine at a molar ratio of 1:2 at 60 °C until a homogeneous liquid was obtained.[21]

The thereby obtained the DES was characterized by Fourier Transform Infrared (FTIR) spectroscopy (**Figure 3A**). The FTIR spectra of both DES and their two precursors (FeCl$_3$·6H$_2$O and meglumine) were recorded and put together in order for us to find any changes. The bottom blue line is for DES, the top black line is for FeCl$_3$·6H$_2$O, and the meddle red line is for meglumine. The peaks at about 2950 cm^{-1}, 2850 cm^{-1} and 1450 cm^{-1} can be ascribed to C–H symmetric stretching, C–H asymmetric stretching and the CH$_2$ bending vibration, respectively.[22] The peaks at about 3327 cm^{-1} and 3239 cm^{-1} can be assigned to stretching vibration of N–H band and O–H

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bond of meglumine.[23] An intermolecular interaction between $FeCl_3\cdot 6H_2O$ and meglumine can be verified by the broaden peaks at around these areas. And the peaks at about 1087 cm^{-1} and 1054 cm^{-1} can be assigned to C–O stretching vibration of meglumine. In $FeCl_3\cdot 6H_2O$/meglumine system, a slight red shift occurred, and the peaks appeared at 1078 cm^{-1} and 1038 cm^{-1}, respectively. This result suggested that the DES are indeed formed by the coordination between $FeCl_3\cdot 6H_2O$ and meglumine. Moreover, at a loading below 50 wt%, the amount of water has no significant effect on the formation of DES (see SI, **Figure S1**).[24]

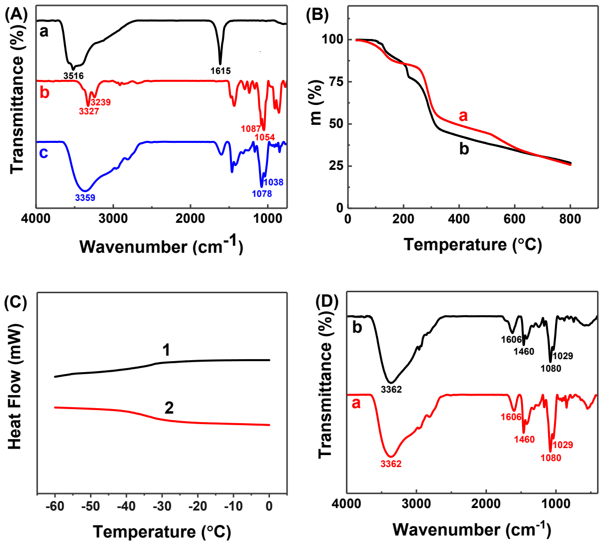

Figure 3. FTIR spectroscopy of (a) $FeCl_3\cdot 6H_2O$ by liquid film; (b) meglumine by KBr; (c) $FeCl_3\cdot 6H_2O$/ meglumine DES by liquid film (A); TGA analysis of (a) fresh $FeCl_3\cdot 6H_2O$/meglumine DES; (b) recovered $FeCl_3\cdot 6H_2O$/meglumine DES under Argon atmosphere (B); DSC of $FeCl_3\cdot 6H_2O$/meglumine DES (line 1: the first scan, line 2: the second scan) (C); FTIR spectroscopy of (a) fresh $FeCl_3\cdot 6H_2O$/meglumine DES by liquid film; (b) recovered $FeCl_3\cdot 6H_2O$/meglumine DES by liquid film (D).

Thermal stability of the DES was investigated by TGA analysis, and the results are depicted in **Figure 3B**. Under mild conditions, a temperature ranging from 25 °C to 80 °C, the weight of $FeCl_3\cdot 6H_2O$/meglumine DES keeps nearly unchanged. The weight loss from 80 °C to about 200 °C can be ascribed to the evaporation of moisture and the decomposition of crystal water in $FeCl_3\cdot 6H_2O$.[25] The weight loss from 200 °C to about 330 °C can be linked to the decomposition of meglumine as meglumine starts to decompose about 200 °C.[26] The obtained TGA data indicated that $FeCl_3\cdot 6H_2O$/meglumine DES has a quite good thermal stability under mild conditions (< 80 °C), and can thus be applied as solvent or catalyst in a reaction. The differential scanning calorimeter (DSC) was used to investigate the thermal behavior of $FeCl_3\cdot 6H_2O$/meglumine DES, and the DSC curves from -60 °C to 0 °C are given in **Figure 3C**. Only one endothermic peak or exothermic peak in DSC curve can be observed and they are located in nearly the same temperature range. It may be connected with higher rates of relaxation of the structure of DES from liquid to grass state while cooling.[27] This result indicated that no phase change appeared and only a glass transition temperature was observed at about -30 °C for $FeCl_3\cdot 6H_2O$/meglumine DES.

We then used the DES in the three-component reaction of indole, glycolaldehyde diethyl acetal and ethyl acetoacetate as dual solvents/catalysts. Some well-known DESs were also examined. In order to check the water compatibility of the newly developed DES catalytic system, water was also added (50 wt% with respected to the weight of DES). The reaction was performed at 60 °C in the presence of 5 mol% of DES-water mixtures. The obtained results were tabulated in **Table 2**. No reaction occurred when ChCl/ethylene glycol (1:2)-H_2O was used (entry 1). This is quite reasonable as ChCl/ethylene glycol DES was known as a neutral DES.[28] When $ZnCl_2$/ethylene glycol (1:2)-H_2O was used, **4a** can be isolated in 14% yield (entry 2). The reaction with $FeCl_3\cdot 6H_2O$/ethylene glycol (1:2)-H_2O gave nearly the same result (entry 3). In these DESs-mediated reactions, the formation of **5a** can be clearly observed. A significant yield improvement was observed by changing the HBD component from ethylene glycol to glycerol. The reaction with $FeCl_3\cdot 6H_2O$/glycerol (1:2)-H_2O gave the desired **4a** in 43% yield (entry 4). The side reaction toward the formation of **5a** was also improved, but not as much as the **4a**-forming reaction. A novel DES-water mixture, $FeCl_3\cdot 6H_2O$/meglumine (1:2)-H_2O, can also promote the reaction efficiently, and a fairly good yield of **4a**, 46%, can be obtained (entry 5). In order to further improve the reaction yield, we tried to increase the loading of $FeCl_3\cdot 6H_2O$/meglumine (1:2)-H_2O. When it was used in 15 mol%, the yield of **4a** can be improved to 63% (entry 6). By performing the reaction at 80 °C, a yield up to 73% can be achieved (entry 7). In these cases, the formation of by-product **5a** proceeded also inevitably. Fortunately, this side reaction consumed only a small part of substrate, thus the **4a**-forming reaction remains to be predominant. The molar ratio of HBA/HBD is also an important parameter to determine the catalytic activity of $FeCl_3\cdot 6H_2O$/meglumine-H_2O. The optimal molar ratio of $FeCl_3\cdot 6H_2O$/meglumine was proved to be 1:2 (entries 7, 8 and 9). Additionally, we have tested $FeCl_3\cdot 6H_2O$ in the model reaction. When 15 mol% $FeCl_3\cdot 6H_2O$ was directly used, a complex messy mixture was obtained, in which the desired product **4a** was hardly observed by TLC detection after 10 h of reaction at 80 °C. So we think the DES structure is indeed pivotal in the catalysis.[29] On the basis of all these studies, a DES-based method **C** was established to implement the synthesis of **4a**: $FeCl_3\cdot 6H_2O$/meglumine (1:2)-H_2O (50 wt% with respect to the weight of DES) (15 mol%), 80 °C, and 10 h. It should be noted that, without adding water component, $FeCl_3\cdot 6H_2O$/meglumine DES can also catalyze the reaction very well, and the yield of **4a** reached 72% under the identical conditions (entry 10). In fact, even 300 wt% of water was added, the reaction still proceeded very well with the aid of $FeCl_3\cdot 6H_2O$/meglumine DES, and the yield of **4a** reached 67% (see SI, **Figure S2**). This result manefasted that $FeCl_3\cdot 6H_2O$/meglumine DES might be indeed a suitable catalytic system to update bio-based water-containing glycolaldehyde to value-added products.

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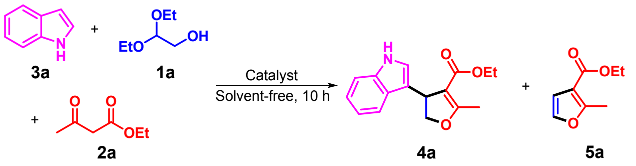
Table 2. Three-component reaction of **1a**, **2a** and **3a** in DES-water mixtures.[a]



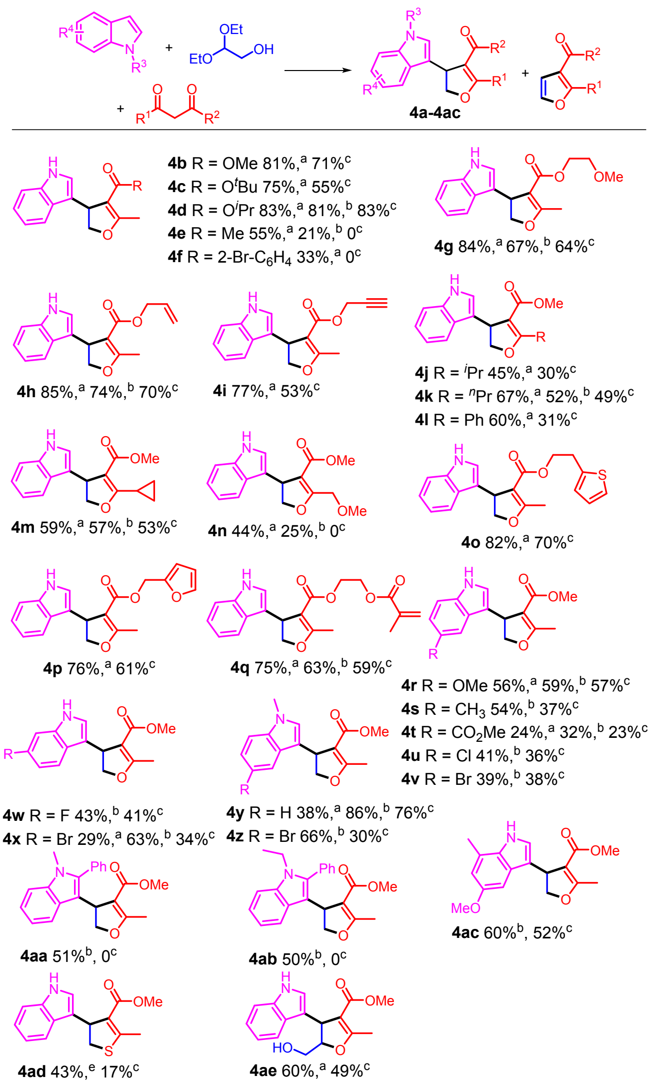
entry	catalyst and specified conditions	yield (%)[b]	
		4a	**5a**[c]
1	ChCl/ethylene glycol (1:2)-H_2O (5 mol%), 60 °C	0	0
2	$ZnCl_2$/ethylene glycol (1:2)-H_2O (5 mol%), 60 °C	14	17
3	$FeCl_3{\cdot}6H_2O$/ethylene glycol (1:2)-H_2O (5 mol%), 60 °C	16	21
4	$FeCl_3{\cdot}6H_2O$/glycerol (1:2)-H_2O (5 mol%), 60 °C	43	24
5	$FeCl_3{\cdot}6H_2O$/meglumine (1:2)-H_2O (5 mol%), 60 °C	46	22
6	$FeCl_3{\cdot}6H_2O$/meglumine (1:2)-H_2O (15 mol%), 60 °C	63	26
7	$FeCl_3{\cdot}6H_2O$/meglumine (1:2)-H_2O (15 mol%), 80 °C (method **C**)	73	25
8	$FeCl_3{\cdot}6H_2O$/meglumine (1:1)-H_2O (15 mol%), 80 °C	0	0
9	$FeCl_3{\cdot}6H_2O$/meglumine (1:3)-H_2O (15 mol%), 80 °C	12	15
10	$FeCl_3{\cdot}6H_2O$/meglumine (1:2) (15 mol%), 80 °C	72	23
11	$FeCl_3{\cdot}6H_2O$ (15 mol%), 80 °C	0	0

[a]: **1a** (0.4 mmol), **2a** (0.4 mmol), **3a** (0.2 mmol), water (50 wt%) was added in DESs. [b]: Isolated yield, and calculated with respect to **3a**. [c]: Isolated yield, and calculated with respect to **1a**.

Having three different methods in hand, we studied the scope of substrate, and the results are given in **Scheme 1**. A wide range of β-ketoesters were used to assemble with **1a** and indole **3a**. Three methods are all effective to promote the reactions, and the corresponding dihydrofurans were obtained in generally good yields (**4b–d**, **4g–m**, and **4o–q**). When the reactions were performed in organic solvents, as evidenced by the results in **Scheme 1**, method **A** displayed superior catalytic ability than method **B**. Double and triple bonds, ether and acrylate moiety can all be delivered uneventfully into the product molecules (**4g–4i**, **4q**). An acid-liable cyclopropyl-containing β-ketoeaster is also amenable to this three-component reaction, affording the desired product **4m** in > 53% yield. β-Ketoesters with a heterocyclic group, such as furan-2-yl and thiophene-2-yl, are also applicable in this reaction, and the desired dihydrofurans **4o** and **4p** were obtained in quite good yield. In all the reactions of β-ketoesters, method **C** that involves the use of DES as dual solvent/catalyst seems slightly less effective compared with method **A** and **B**. This can also be verified by the reactions of 1,3-diketones. While the expected products can be obtained in at maximum moderate yields with methods **A** and **B**, only by-product furans were isolated with method **C**. (**4e–f**, **4n**). However, limitations of this three-component reaction were also observed. Attempts to use ethyl trifluoroacetoacetate and ethyl 4-chloroacetoacetate as substrate failed.

We also probe the scope of the reaction with respect to indole component. In most of the cases, three methods were used in order for us to find the best system for each individual reaction. As shown in **Scheme 1**, indoles with different substituents smoothly reacted with **1a** and **2a**, producing dihydrofuran products in fairly good yields. Both electron-rich and moderately electron-poor indoles readily participated in the reaction. However, those containing strongly electron-withdrawing groups, such as 5-cyanoindole and 5-nitroindole, failed to participate in the reaction. Different from the results obtained in extending the scope of 1,3-dicarbonyl component, the performance of method **A** is not always superior to method **B**. In the synthesis reactions of **4x** and **4y**, the yields obtained with method **B** are even twice higher than that of method **A**. In many cases, the yields obtained with method **C** are comparable with that obtained with organic solvent systems. However, when 2-phenylindoles were used, method **C** was found to be invalid perhaps due to the strong hydrophobicity of the indole compounds. Then we continued to explore the reactivity of glycolaldehyde analogues in the model reaction. When (4R)-2,2-dimethyl-1,3-dioxolane-4-carboxadehyde was used, the desired dihydrofuran **4ad** was obtained with method **A** and method **C** in quite good yield. Method **A** slightly displayed superior catalytic ability than method **B**. And 2,5-dihydroxy-1,4-dithiane was also applicable in this reaction to obtain 2,3-dihydrothiophene derivative.

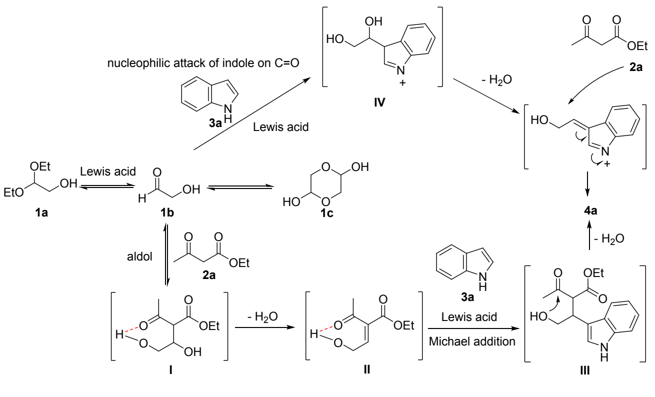
It should be noted that the dihydrofuran ring system is found prevalently at the central position of diverse classes of naturally occurring and biologically active heterocycles.[30] A plenty of syntheses of dihydrofurans are available which offers a variety of intermediates and reaction conditions.[31] A large majority of synthetic approaches have been accomplished via ionic[32] or radical pathways[33] through oxidative addition of 1,3-dicarbonyl compounds to appropriate olefins. Although all of these methodologies afford the dihydrofuran moiety in a reasonable yield, simple and efficient synthetic approaches still remain scarce.[34] The present reaction offered thus an expedient method to synthesize dihydrofurans with an indo-3-yl substituent, which cannot be attained with the other methods.



[a]: **1a** (0.4 mmol), **2a** (0.4 mmol), **3a** (0.2 mmol), method **A**: Sc(OTf)$_3$ catalyst (5 mol%), r.t., nitromethane (1.0 mL), 1 h. [b]: **1a** (0.4 mmol), **2a** (0.4 mmol), **3a** (0.2 mmol), method **B**: Ni(ClO$_4$)$_2$·6H$_2$O catalyst (20 mol%), 80 °C, acetonitrile (1.0 mL), 6 h. [c]: **1a** (0.4 mmol), **2a** (0.4 mmol), **3a** (0.2 mmol), method **C**: FeCl$_3$·6H$_2$O/meglumine-H$_2$O (15 mol%), 80 °C, 10 h. [e]: **1a** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.2 mmol), method **C**: MnBr$_2$ catalyst (20 mol%), 80 °C, acetonitrile (1.0 mL), 12 h.

Scheme 1. Substrate scope of three-component reaction of indoles, glycolaldehyde acetal and 1,3-dicarbonyl compounds.

A mechanism was also proposed as depicted in **Scheme 2**. Initial event of the reaction should be an acid-catalyzed deacetalization of **1a**, leading to the formation of glycolaldehyde **1b**. This species can be trapped by **3a** or **2a**. It can also be converted reversibly to its dimer **1c**. Assembly of **1b** with **2a** through an aldol-type reaction occurred, and resulting in the generation of an intermediate **I** (the bottom pathway). An intramolecular hydrogen bond between the hydroxyl group and the ketone carbonyl may be formed in this intermediate. This increased the stability of **I**, conferring thus **2a** a priority to interact with **1b** compared with **3a** (the upper pathway). A Knoevenagel product **II** was then formed, which can be trapped by **3a** through a Michael addition. The resulted intermediate **III** underwent an intramolecular dehydration, affording thus **4a** as the final product. The last step should be very fast, otherwise this three-component reaction wouldn't be successful. Michael addition of **3a** to intermediate **II** may be crucial, and if it is insufficient, the equilibria of the reaction will channelize to the formation of **5a**. Considering together with the reactant scope, we found that indoles with moderate and strong electron-withdrawing including 5-cyanoindole and 5-nitroindole, failed to participate in the reaction, because of their weakly nucleophilicity.



Scheme 2. Proposed mechanism of a three-component reaction.

In fact, the real advantages of using the DES as dual solvent/catalyst in the title reaction came from considering the following factors: (i) recyclability and (ii) feasibility of using an aqueous solution of glycolaldehyde. To investigate the recyclability, the progress of a three-component reaction driven by FeCl$_3$·6H$_2$O/meglumine was recorded by a camara, and the pictures were collected in **Figure 4**. The DES is a dark brown fluid (Fig. 4a). After adding all of the starting materials, owing to the high viscosity of the DES at room temperature, a biphasic system could be visually observed (Fig. 4b). During the reaction, a homogeneous liquid was formed (Fig. 4c). At the end of the reaction, the formed products can be isolated through extraction with a mixture compose of heptane and ethyl acetate (H/E$_{v/v}$ = 5:1) (Fig. 4d). The DES can thus be recovered and reused. Then we investigated the recycling performance of DES in the model reaction. The results are shown in **Table 3**. After four consecutive runs, the FeCl$_3$·6H$_2$O/meglumine is still capable of catalyzing the model reaction in 64% yield. TGA analysis revealed that the weight losses of fresh and recovered FeCl$_3$·6H$_2$O/meglumine DES remained consistent (**Figure 3B**). By comparing FT-IR spectra of fresh and recovered FeCl$_3$·6H$_2$O/meglumine DES (**Figure 3D**), it can be found that the absorption peaks almost had no change. The DSC curves of fresh and recovered FeCl$_3$·6H$_2$O/meglumine DES exhibited the same glass transition temperature (see SI, **Figure S3**). The results indicate that FeCl$_3$·6H$_2$O/meglumine DES is indeed stable and recyclable in the model synthesis reaction.

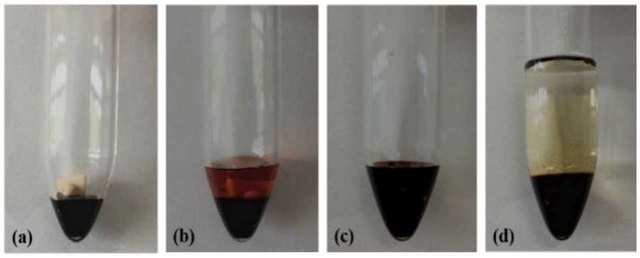


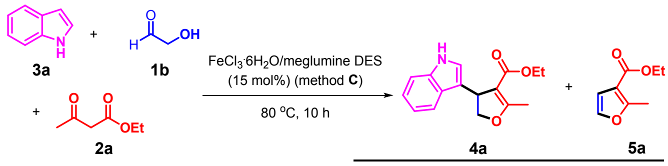
Figure 4. Progress of the model reaction in the DES. (a) $FeCl_3 \cdot 6H_2O$/meglumine DES; (b) after adding all of the starting materials; (c) at the end of the reaction; (d) product extraction with organic solvent.

Table 3. Reusability of $FeCl_3 \cdot 6H_2O$/meglumine DES.[a]

Run	1	2	3	4
Yield (%) **4a**	73	67	65	64

[a]: Method **C**: **1a** (0.4 mmol), **2a** (0.4 mmol), **3a** (0.2 mmol), $FeCl_3 \cdot 6H_2O$/meglumine DES (15 mol%), 80 °C, 10 h.

To investigate the feasibility of using bio-based glycolaldehyde, commercially available glycolaldehyde was dissolved in water to prepare two solutions with different concentrations (25 wt% and 50 wt%) and then utilized in the three-component reaction. As shown in **Scheme 3**, the reaction with an aqueous solution of glycolaldehyde (25 wt%) proceeded very well with the aid of $FeCl_3 \cdot 6H_2O$/meglumine DES, producing **4a** in 51% yield after 10 h of reaction at 80 °C. When a concentrated solution of glycolaldehyde (50 wt%) was used, the yield keeps almost constant. However, in an organic system, $Sc(OTf)_3$/nitromethane, the aqueous solution of glycolaldehyde can be hardly used, and the yield of **4a** reached only 8%. And $Ni(ClO_4)_2 \cdot 6H_2O$/acetonitrile worked slightly, and the yield of **4a** can be improved to 26%. These results demonstrated that using $FeCl_3 \cdot 6H_2O$/meglumine as dual solvent/catalyst indeed enabled the utilization of bio-based glycolaldehyde in the model three-component assembly reactions. We found also that the DES can be recycled and reused in this reaction, and the catalytic activity remained perfect in the second run.



Entry	Glycolaldehyde	Yield (%)	
		4a	**5a**
1[a]	25 wt% *aqu.*	8	0
2[b]	25 wt% *aqu.*	26	27
3	25 wt% *aqu.*	51	13
4	50 wt% *aqu.*	47	15
5[c]	25 wt% *aqu.*	50	10

[a] $Sc(OTf)_3$/nitromethane(method **A**).
[b] $Ni(ClO_4)_2 \cdot 6H_2O$/acetonitrile (method **B**).
[c] Recovered DES was used.

Scheme 3. A three-component reaction of using bio-based glycolaldehyde aqueous solution in the $FeCl_3 \cdot 6H_2O$/meglumine DES.

Conclusions

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To update the use of bio-based glycolaldehyde, a hydrolysis product of cellulose or glucose, as a platform molecule towards value-added products, we first developed an expedient three-component reaction of indole, glycolaldehyde acetal and 1,3-dicarbonyl compound in organic solvent systems. Both $Sc(OTf)_3$ and $Ni(ClO_4)_2 \cdot 6H_2O$ are able to catalyze the reaction efficiently, providing a hitherto unreported class of 3-(indol-3-yl)-2,3-dihydrofurans in good to excellent yields. We then turned to aqueous systems for which the previous conditions were not giving satisfactory results. To enable the use of aqueous solution of glycolaldehyde, we developed a novel DES, $FeCl_3 \cdot 6H_2O$/meglumine. This system was proved to be an efficient and a water-compatible promoting medium for the synthesis of dihydrofuran derivatives via the three-component reaction. The use of bio-based glycolaldehyde as starting material is also very successful. The system can also be recycled without significant loss of its activity. This work may give an inspiration to organic chemists that bio-based glycolaldehyde should be a useful C2 building block, which has unique reactivities and can be hopefully applied in many organic transformations. In the future, much effort should be paid to (i) explore suitable methods for large scale synthesis of bio-based glycolaldehyde, and (ii) develop appropriate catalytic systems for enabling the use of water-containing bio-based glycolaldehyde.

Experimental

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-400. Chemical shifts are expressed in parts per million relative to Me_4Si in $CDCl_3$ or DMSO-d_6. IR spectra were recorded with a FT-IR Bruker (EQUINOX 55) spectrometer using KBr pellets or neat liquid. The thermal stability of the samples was characterized by thermogravimetric analysis (TGA, TGA-7, Perkin-Elmer, USA) at a heating rate of 10 °C min^{-1} in an argon flow (20 mL min^{-1}). Differential scanning calorimetry (DSC) measurements were conducted in a DSC Q2000 (Thermal Analyst Co., TA Instruments, USA) to determine the glass transition temperature (T_g) of DESs. All experiments were performed from 30 °C to -60 °C at a heating rate 10 °C min^{-1} in an argon atmosphere at 50 mL min^{-1}.

Synthesis of ***3i, 3o*** *and* ***3p***: a solution of methyl acetoacetate (2 mmol) in toluene was mixed with propargyl alcohol (2 mmol) and triphenylphosphine (0.2 mmol) to obtain (2-propynyl) 3-oxobutanoate (**3i**).[35] The mixture was then refluxed for 6 h. The progress of the reactions was monitored by TLC. After the reaction, the reaction mixture was cooled to room temperature, and the product was obtained in 83% yield by isolation with preparative TLC (eluting solution: petroleum ether/ethyl acetate = 5/1 (v/v)). Synthesis of the other compounds was performed by an analogous procedure.

Synthesis of ***4a*** *and* ***5a****:* the reaction was conducted in a 10 mL V-type flask equipped with a triangular magnetic stirring bar. A solution of ethyl acetoacetate (0.4 mmol) in CH_3NO_2 (1.0 mL) was mixed with glycolaldehyde diethyl acetal (0.4 mmol), indole (0.2 mmol) and $Sc(OTf)_3$ (0.01 mmol) to obtain target product (**4a**). The mixture was then stirred at room temperature for 1 h. After the reaction, the product was obtained in 81% by isolation with preparative TLC (eluting solution: petroleum ether/ethyl acetate = 5/1 (v/v)). All tests for substrate scope were performed with an analogous procedure (method **A**). And a solution of ethyl acetoacetate (0.4 mmol) in CH_3CN (1.0 mL) was mixed with glycolaldehyde diethyl acetal (0.4 mmol), indole (0.2 mmol) and $Ni(ClO_4)_2{\cdot}6H_2O$ (0.08 mmol) to obtain target product (**4a**). The mixture was then stirred at 80 °C for 6 h. After the reaction, the mixture was cooled to room temperature, and the product was obtained in 79% by isolation with preparative TLC (eluting solution: petroleum ether/ethyl acetate = 5/1 (v/v)). All tests for substrate scope were performed with an analogous procedure (method **B**). And a solution of ethyl acetoacetate (0.4 mmol) was mixed with glycolaldehyde diethyl acetal (0.4 mmol), indole (0.2 mmol) and $FeCl_3{\cdot}6H_2O$/meglumine-H_2O (0.03 mmol) to obtain target product (**4a**). The mixture was then stirred at 80 °C for 10 h. After the reaction, the mixture was cooled to room temperature, and the product was obtained through extraction with a mixture compose of heptane and ethyl acetate (H/Ev/v = 5:1). And then the formed products can be isolated with preparative TLC (eluting solution: petroleum ether/ethyl acetate = 5/1 (v/v)) (method **C**).

Conflicts of interest

The authors declare no competing financial interest.

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