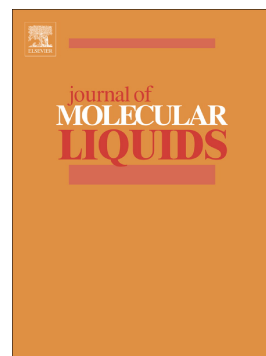


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Synthesis of glyceryl monocaffeate using ionic liquids as catalysts

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Abstract

Glyceryl monocaffeate (GMC) is the hydrophilic derivative of caffeic acid (CA), which can be used in cosmetic and food industries. In this paper, GMC was prepared by the reaction of glycerol with different caffeoyl donors (CA, or ethyl caffeic (EC)). Seven functionalized ionic liquids ([PSO₃HMIM]HSO₄, [BSO₃HMIM]TS, [BSO₃HMIM]OTf, [BSO₃HMIM]HSO₄, [AAMIM]HSO₄, [BSO₃HMIM]HPO₄ and [HMIM]HSO₄) were used as catalysts. Effects of reaction variables (reaction temperature, time, pressure, catalyst load and molar ratio of substrates) on CA conversion and GMC yield were investigated. For the esterification of glycerol with CA, high CA conversion (95.6±2.1%) and GMC yield (93.8±3.2%) were achieved using [BSO₃HMIM]TS as catalyst under the following conditions: 90°C, CA/glycerol 1:10 (mol/mol), catalyst load 10% (relative to the weight of all substrates), 2h. Activation energies (E_a) of CA conversion and GMC formation were 84.53 kJ/mol and 86.67 kJ/mol, respectively, which were lower than those (111.79, 116.24 kJ/mol) of EC as caffeoyl donor.

Keywords: Caffeic acid; Glycerol; Glyceryl monocaffeate; Ionic liquid; Esterification;

Activation energy

1. Introduction

Caffeic acid (3,4-dihydroxycinnamic acid, CA) is a naturally phenolic compound, which can be found throughout the plant kingdom (fruits, cereals, coffees and vegetables) [1,2]. Recently, CA and its derivatives have attracted extensive attentions due to its biological functions, for examples, UV-absorption [3,4], antimicrobial, anti-inflammatory [5], antioxidant [6-8], antiviral [9], and antitumor activities [10-12]. However, the low solubility of CA in polar/non-polar media limits its application in hydrophilic and lipophilic systems. Therefore, modifications of CA have been necessary for the wide application of CA in food, cosmetics and pharmaceutical industries [13-16].

Glyceryl monocaffeate (GMC) is a kind of hydrophilic ester of CA. The solubility of GMC is 3 times that of CA in water at 20°C [17]. In the previous report [17], GMC was prepared by the transesterification of ethyl caffeic (EC) with glycerol using Novozym 435 as catalyst. And EC was used as caffeoyl donor, which firstly needed the preparation of EC by the esterification of CA and ethanol. In order to efficiently prepare GMC, different reaction strategies have attracted more attention.

Ionic liquids (ILs), one kind of salts composed of organic cations and inorganic or organic anions, have been used as promising solvents and catalysts [18,19]. As one kind of novel catalysts, ILs have many advantages, such as, low melting point, negligible vapor pressure, non-flammability, and high catalytic activity, etc [20-24]. In our group, ILs have been used as catalysts to prepare biodiesel and ricinoleic acid estolides [25,26], and we also used ILs as reaction media for some enzymatic reactions [27,28]. However, to the best of our knowledge, ILs used as catalyst for GMC preparation was not found.

In the work, ILs were used as catalysts to catalyze the esterification of CA with glycerol for GMC preparation, which was compared with that of EC as caffeoyl donor. Seven ILs were selected and compared in the esterification. Effects of reaction variables (reaction temperature, pressure, reaction time, catalyst load and substrate ratio) on the reaction were investigated. Reaction thermodynamics were also evaluated.

2. Experimental section

2.1. Materials and reagents

Caffeic acid (CA, purity > 99%) and ethyl caffeate (EC, purity > 99%) were purchased from Nanjing Zelang Chemical Co., Ltd. (Nanjing, China). Glycerol (purity > 99%, dehydration using activated molecular sieves before used) was from Tianjin Kermel Chemical Co., Ltd. (Tianjin, China). Ionic liquids (1-butylsulfonic-3-methylimidazolium tosylate, [BSO₃HMIM]TS; 1-propylsulfonic-3-methylimidazolium hydrogen sulfate, [PSO₃HMIM]HSO₄; 1-butylsulfonic-3-methylimidazolium trifluoromethanesulfonate, [BSO₃HMIM]OTf; 1-butylsulfonic-3-methylimidazolium hydrogen sulfate, [BSO₃HMIM]HSO₄; *N*-methylimidazolium hydrogen sulfate, [HMIM]HSO₄; 1-butylsulfonic-3-methylimidazolium hydrogen phosphate, [BSO₃HMIM]HPO₄; 1-carboxymethyl-3-methylimidazolium hydrogen-sulfate, [AAMIM]HSO₄) were purchased from Shanghai Cheng Jie Chemical Co., Ltd. (Shanghai, China). The purities of these ionic liquids were all above 99%. H₂SO₄, *p*-TSA, methanol (HPLC grade) and glacial acetic acid (HPLC grade) were provided by Tianjin Kermel Chemical Co., Ltd. (Tianjin, China). All other solvents were of analytical grade.

2.2. Esterification of CA with glycerol or transesterification of EC with glycerol

The reaction of 10 mmol glycerol with 1mmol CA (or EC) was conducted in 25 mL round-bottom flasks. Reaction mixtures were catalyzed by various catalysts (ILs, H₂SO₄ or *p*-TSA), and incubated at different temperatures using oil bath at 250 rpm. Samples (5uL) were withdrawn periodically using a micro pipettor and then mixed with 3 mL ethanol.

2.3. Analytical Techniques

The reactants and products were analyzed by HPLC (waters 1525) with a C18 reverse phase column (5 μ m, 250 mm \times 4.6 mm) according to our previous report [17]. The elution was achieved with solvent A (methanol, 100%) and solvent B (water containing 0.5% glacial acetic acid) at 1 mL/min. The elution sequence was a linear gradient from 20% (v/v) B to 100% (v/v) B over 18 min, and then to 20% (v/v) B in 4 min followed by 20% (v/v) B for 4 min. The eluate was monitored at 325 nm using a dual absorbance detector (waters 2489).

2.4. Statistical analysis

In order to ensure the validity of results, all experiments were carried out at least in triplicate. Results were expressed as averages \pm SEM. The significance of the difference was evaluated using a two-way analysis of variance (ANOVA). Statistical significance was considered at $p < 0.05$.

3. Results and discussion

3.1. Effect of reaction pressure

In the study, byproduct (water or ethanol) was formed by the esterification of CA with glycerol or transesterification of EC with glycerol. In theory, the removal of byproduct at vacuum can favor the reaction towards GMC formation. However, the effect of reaction pressure on the

reaction of CA (or EC) with glycerol (**Figure 1A**) actually was different from the theoretical results. Initial CA conversion of vacuum pressure rapidly increased to $94.2 \pm 1.5\%$ for 1.5h, which was similar to that ($92.9 \pm 2.5\%$) of the atmospheric pressure. But CA conversion sharply declined to $29.2 \pm 2.2\%$ with experiment proceeding. GMC yield initially increased to $91.8 \pm 1.6\%$, and then decreased to $25.1 \pm 2.8\%$ (12h) under vacuum system, which was lower than that ($91.6 \pm 1.2\%$) of atmospheric pressure. Results could be explained by the fact that the removal of water will affect the release of dissociate protons from ILs and then decrease the catalytic activities of ILs. Similar effect of water on the activity of IL can also be found in other reaction [26]. For the transesterification of EC with glycerol, there was no significant difference under vacuum pressure ($92.7 \pm 1.5\%$) and atmospheric pressure ($92.3 \pm 2.9\%$) for 8h (**Figure 1B**). However, the GMC yield ($88.6 \pm 2.6\%$) of atmospheric pressure was higher than that ($30.1 \pm 1.2\%$) of vacuum pressure at 12h. The phenomenon was different from that of the enzymatic transesterification of EC with glycerol (the more vacuum the more GMC yield) [17]. Therefore, atmospheric pressure system was the best choice for ILs-catalyzed the esterification of CA with glycerol.

3.2. Catalyst performance of ILs

The acidity of catalyst had a significant effect on its activity, which was significant dependent on the structure of cations, anions and attached alkyl functional groups [30-32]. The effect of various ILs or inorganic acids (H_2SO_4 or *p*-TSA) on the esterification of CA with glycerol was shown in **Figure 2A**. When the anion of ILs was HSO_4^- , CA conversion increased in the order of $[\text{BSO}_3\text{HMIM}]\text{HSO}_4 > [\text{PSO}_3\text{HMIM}]\text{HSO}_4 > [\text{AAMIM}]\text{HSO}_4 > [\text{H}_2\text{SO}_4] > [\text{HMIM}]\text{HSO}_4$. The results may be explained by the fact that the higher acidity of $[\text{BSO}_3\text{HMIM}]^+$ and $[\text{PSO}_3\text{HMIM}]^+$

containing both $-\text{SO}_3\text{H}$ and HSO_4^- group than those of $[\text{AAMIM}]^+$ and $[\text{HMIM}]^+$ with only HSO_4^- group (Table 1) [30,33,34]. The high activity of $[\text{BSO}_3\text{HMIM}]\text{HSO}_4$ (CA conversion $> 94.9 \pm 3.1\%$) was ascribed to the presence of long carbon chain of cation, which can dissociate H^+ ion and form stronger activity [35]. In addition, the anion type also affected the esterification of CA. When the cation of ILs was $[\text{BSO}_3\text{HMIM}]^+$, the ILs with TS^- , OTF^- or HSO_4^- all gave outstanding catalytic performance (CA conversion $> 94\%$, GMC yield $> 92\%$). However, ILs with HPO_4^- exhibited poor activity (CA conversion $< 15\%$, GMC yield $< 15\%$). This may be due to the weak acidity of HPO_4^- [36].

Although the transesterification of EC with glycerol also exhibited high EC conversion ($> 88\%$) using $[\text{BSO}_3\text{HMIM}]\text{OTF}$, $[\text{BSO}_3\text{HMIM}]\text{TS}$, $[\text{BSO}_3\text{HMIM}]\text{HSO}_4$, $[\text{PSO}_3\text{HMIM}]\text{HSO}_4$ and H_2SO_4 as catalysts, GMC yields were lower than 85% (**Figure 2B**). This was probably ascribed to the enhancement of the side effect resulting from strong acidity of HSO_4^- based ILs. In consideration of GMC yield and catalyst miscibility with substrates, $[\text{BSO}_3\text{HMIM}]\text{TS}$ was selected as catalyst for further investigation. Compared with EC as caffeoyl donor, the direct esterification of CA with glycerol catalyzed by $[\text{BSO}_3\text{HMIM}]\text{TS}$ gave higher GMC yield ($95.1 \pm 1.8\%$) and reaction rate, which could be explained that CA has better compatibility with glycerol and lower steric hindrance than that of EC.

3.3. Effect of reaction temperature

High temperature decreased the viscosity of reaction system, and accelerated the diffusion of reactants and reaction rate. However, excessive high temperatures resulted in the formation of byproducts. The esterification of CA with glycerol was conducted at different temperatures varying from 50 - 110°C . When the temperature was 50°C , only $30.9 \pm 2.7\%$ CA conversion was

obtained at 22h (**Figure 3A**). The increase of temperature can enhance CA conversion and GMC formation. For example, high CA conversion ($95.1 \pm 3.1\%$) and GMC yield ($92.9 \pm 2.9\%$) can be achieved at 90°C and 2h (**Figure 3B**). This results were attributed to the low viscosity of reaction system and fast mass transfer rate at high temperature [37]. However, when the temperature increased up to 110°C , CA conversion had no significant change ($\sim 95\%$) and GMC yield decreased to $84.2 \pm 2.7\%$ after 8h, which may be ascribed to more byproduct formation from oligomerization or polymerization. This results were also in accordance with the experimental phenomenon that the reaction mixture became dark and high viscosity appeared at high temperature ($>90^\circ\text{C}$). When EC was used as caffeoyl donor, high GMC yield ($87.1 \pm 2.7\%$, 90°C) was obtained (**Figure 3D**). However, GMC yield after equilibrium decreased to $21.9 \pm 3.1\%$, when reaction temperature increased to 90°C , which was ascribed to more CA and glyceryl dicaffeates (GDC) formation at high temperature ($>90^\circ\text{C}$). Therefore, 90°C was selected as the optimum reaction temperature.

The initial esterification rate of CA with glycerol increased with the increase of temperature from 50 to 110°C (**Figure 4A**). A good liner relationship was obtained by a plot of $\ln V_0$ versus $1/T$. Arrhenius equations of CA conversion and GMC formation could be expressed as $\ln V_0 = 23.744 - 84.53/RT$ and $\ln V_0 = 24.433 - 86.67/RT$, respectively. And the activation energy (E_a) of GMC formation was 86.67 kJ/mol, which was higher than that (84.53 kJ/mol) of CA conversion (**Figure 4A,B**). However, the E_a of CA conversion (84.53 kJ/mol) was higher than that (69.9 kJ/mol) of the esterification of ferulic acid with glycerol using *p*-TSA as catalyst [38]. This difference was attributed to the great electron-donating and steric hindrance of CA. For the transesterification of EC with glycerol, Arrhenius equations of EC conversion and GMC

formation can be expressed as $\text{Ln}V_0 = 31.537 - 111.79/\text{RT}$ and $\text{Ln}V_0 = 32.877 - 116.14/\text{RT}$. The E_a of EC conversion (111.79 kJ/mol) and GMC formation (116.14 kJ/mol) were higher than those (84.53, 86.67 kJ/mol) of CA as caffeoyl donor, which was attributed to the great steric hindrance of EC and the poor compatibility of EC with glycerol than CA.

3.4. Effect of catalyst load

Catalyst load significantly affected reaction rate and the time at which the reaction reached equilibrium. As can be seen in **Figure 5A** and **Figure 5B**, the increase of catalyst load resulted in the increase of CA conversion and reaction rate, which resulted in a decrease of reaction time to equilibrium. When catalyst load increased up to 10%, CA conversion and GMC yield reached $95.2 \pm 2.2\%$ (**Figure 5A**) and $92.7 \pm 2.8\%$ (**Figure 5B**) at 2h, which was ascribed to the presence of more active site with the increase of catalyst load. However, when catalyst load was above 10%, no significant increase of CA conversion and GMC yield can be found, which indicated that 10% is enough for the esterification of CA with glycerol. Similar to CA as caffeoyl donor, EC conversion increased to $95.4 \pm 1.1\%$ at 12h as catalyst load varied from 2% to 15% (**Figure 5C**). GMC yield increased to $87.1 \pm 2.4\%$ at 6h when catalyst load was up to 10% (**Figure 5D**). However, when catalyst load further increased to 15%, GMC yield decreased to $48.5 \pm 2.9\%$ after 6 h, which was different from that ($\sim 93\%$) of CA as caffeoyl donor. The phenomenon may be due to the formation of more undesired byproducts in the presence of excessive catalyst load.

3.5. Effects of substrate ratio and reaction time

The effect of molar ratio of CA (or EC) to glycerol on the reaction were shown in **Figure 6**. When molar ratio of CA to glycerol was 1:1, CA conversion was lower than 13% at 22 h (**Figure 6A**). When molar ratio of CA to glycerol decreased from 1:1 to 1:5, CA conversion rapidly

reached $84.3 \pm 3.1\%$ and maintained the high level ($\sim 92\%$) after 3h (**Figure 6A**). CA conversion rates were greater than that of EC except for 1:1 (**Figure 6A and 6C**). The increase of glycerol ratio in the reaction system can enhance reaction rate, GMC yield and shorten the time to reach equilibrium. The phenomenon could be explained by the fact that excess glycerol can not only be used as reactant but also as reaction medium, which could reduce the viscosity and the mass transfer resistance of reaction system [17,31]. Similar effect of substrate ratio on GMC yield can also be found from **Figure 6B and Figure 6D**.

As observed in **Figure 7A**, CA conversion increased from $17.9 \pm 2.9\%$ to $95.6 \pm 2.1\%$ with the increase of reaction time from 10min to 2h. The time to reach equilibrium was 2h, which was shorter than that (10h) of the transesterification of EC with glycerol. High CA conversion ($95.6 \pm 2.1\%$) and GMC yield ($93.8 \pm 3.2\%$) of the esterification of CA with glycerol (**Figure 7B**) were achieved under the following conditions: catalyst load 10%, 2h, substrate molar ratio (glycerol to CA) 10:1, and 90°C . The GMC yield was higher than that ($47.2 \pm 2.8\%$) of the transesterification of EC with glycerol at the same conditions.

3.6. Reaction mechanism

In the paper, GMC was successfully prepared by the reaction of CA (or EC) with glycerol using acidic IL ([BSO₃HMIM]TS) as catalyst. According to the catalytic characteristic of acid catalyst [39-41], reaction mechanism using acidic [BSO₃HMIM]TS as catalyst can be proposed as follows (**Figure 8**): firstly, H⁺ was released from the acidic IL ([BSO₃HMIM]TS); secondly, the carbocation was formed by the combination of H⁺ with carbonyl group of CA (or EC); and then, glycerol, as a nucleophile, attacked the carbocation to form one tetrahedron structure; finally, H⁺ and H₂O (or CH₃CH₂OH) were separated from the tetrahedron structure to form GMC.

High reaction selectivity for 1-GMC (1-caffeoyl-sn-glycerol) was ascribed to the steric hindrance of sn-2 hydroxy of glycerol.

4. Conclusions

In the work, GMC, the hydrophilic derivative of CA, was successfully achieved by IL-catalyzed the reaction of glycerol with CA or EC. Among all tested ILs, [BSO₃HMIM]TS showed the best catalytic performance for GMC synthesis. For the esterification of CA with glycerol, high CA conversion ($95.6 \pm 2.1\%$) and GMC yield ($93.8 \pm 3.2\%$) were obtained at 90°C, catalyst load 10%, substrates molar ratio 1:10 (CA/glycerol), 2h. Arrhenius equations for CA conversion and GMC formation were expressed as $\ln V_0 = 23.744 - 84.53/RT$ and $\ln V_0 = 24.433 - 86.67/RT$. Activation energies (E_a) of CA conversion and GMC formation were 84.53 kJ/mol and 86.67 kJ/mol, respectively, which were higher than those (111.79, 116.14 kJ/mol) of EC as caffeoyl donor. Compared with CA as caffeoyl donor, low GMC yield ($47.2 \pm 2.8\%$) was obtained from the transesterification of EC with glycerol at following conditions: 90°C, catalyst load 10%, substrates molar ratio 1:10 (EC/glycerol), 2h.

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Figure captions

Figure 1. (A) Effect of system pressure on the esterification of CA with glycerol. (B) Effect of system pressure on the transesterification of EC with glycerol. Reaction conditions: 10% [BSO₃HMIM]OTF load (relative on the weight of all substrates), glycerol/CA=10:1 (mol/mol), 90°C.

Figure 2. (A) Effect of different ionic liquids as catalysts on the esterification of CA with glycerol. (B) Effect of different ionic liquids as catalysts on the transesterification of EC with glycerol. Reaction conditions: glycerol/CA (or EC) = 10:1, 90°C, 3h, atmospheric pressure, catalyst load 10%.

Figure 3. Effect of temperature on CA conversion (A) and GMC yield (B) when CA was used as acyl donor. Effect of temperature on EC conversion (C) and the GMC yield (D), when EC as acyl donor reacted with glycerol. Reaction conditions: glycerol/CA (or EC) = 10:1, atmospheric pressure, [BSO₃HMIM]TS load 10%.

Figure 4. (A) The relationship between initial rates of CA conversion, EC conversion and reaction temperature. (B) The relationship between initial rates of GMC yields (EC or CA as acyl donor) and temperature. Reaction conditions: glycerol/CA (or EC) = 10:1, atmospheric pressure, [BSO₃HMIM]TS load 10%.

Figure 5. Effect of catalyst load on CA conversion (A) and GMC yield (B). Effect of catalyst load on EC conversion (C) and GMC yield (D). Reaction conditions: atmospheric pressure, glycerol/CA (or EC) = 10:1, 90°C.

Figure 6. Effect of substrate ratio (glycerol/CA, mol/mol) on CA conversion (A) and GMC yield (B). Effect of substrate ratio (glycerol/EC, mol/mol) on EC conversion (C) and GMC yield

(D). Reaction conditions: atmospheric pressure, [BSO₃HMIM]TS load 10%, 90°C.

Figure 7. (A) Effect of reaction time on CA conversion and EC conversion. (B) Effect of reaction time on GMC yields, when CA or EC reacted with glycerol. Reaction conditions: atmospheric pressure, [BSO₃HMIM]TS load 10%, 90°C, molar ratio of glycerol to CA (or EC) 10:1.

Figure 8. Reaction mechanism using acidic [BSO₃HMIM]TS as catalyst of the reaction of CA (or EC) with glycerol to form GMC.

Table 1 H₀ or pH values of catalysts

Ionic liquids or inorganic acids	H ₀ ^a	pH ^b
[BSO ₃ HMIM]TS	1.69	1.95
[BSO ₃ HMIM]OTF	1.94	2.13
[BSO ₃ HMIM]HSO ₄	1.84	2.08
[PSO ₃ HMIM]HSO ₄	1.86	2.10
[AAHMIM]HSO ₄	2.09	2.17
[HMIM]HSO ₄	2.15	2.19
<i>P</i> -TSA ^c	- ^d	1.95
H ₂ SO ₄	- ^d	1.87

^a where indicator: 4-nitroaniline, PK(I)_{aq} = 0.99, solvent EtOH, C(aq) = 30 μmol/L,

C(ILs) = 40 mmol/L.

^b pH values were determined at 18.6 °C, with 10 mmol/L ionic liquid in water.

^c *P*-TSA: *p*-toluene sulfonic acid

^d Not detected.

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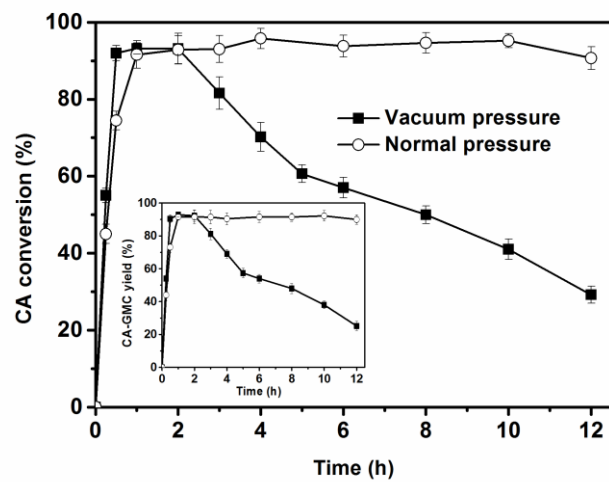
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Figure 1

(A)



(B)

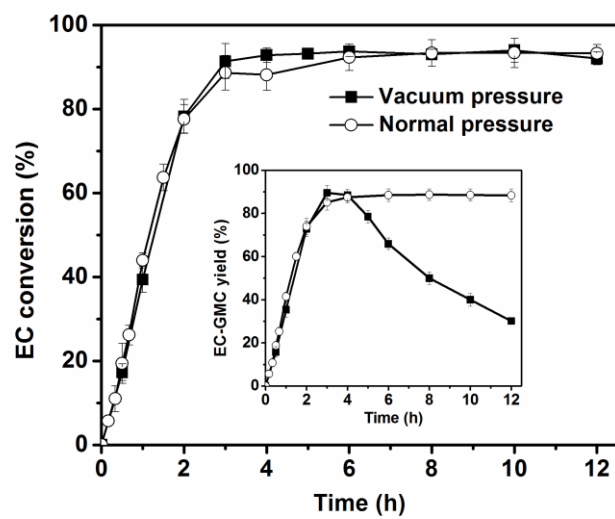
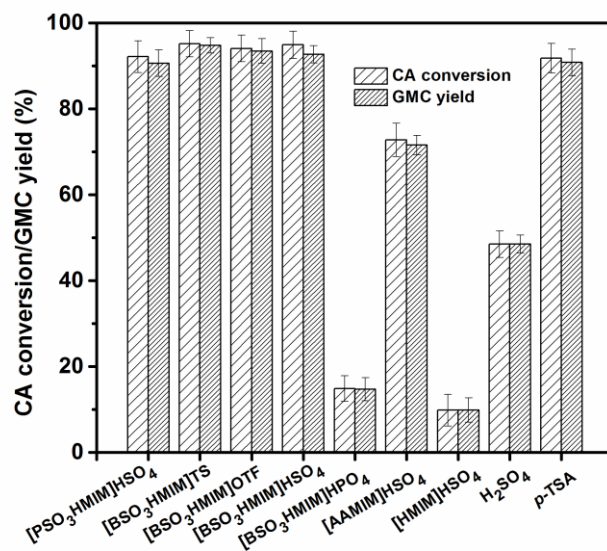


Figure 2

(A)



(B)

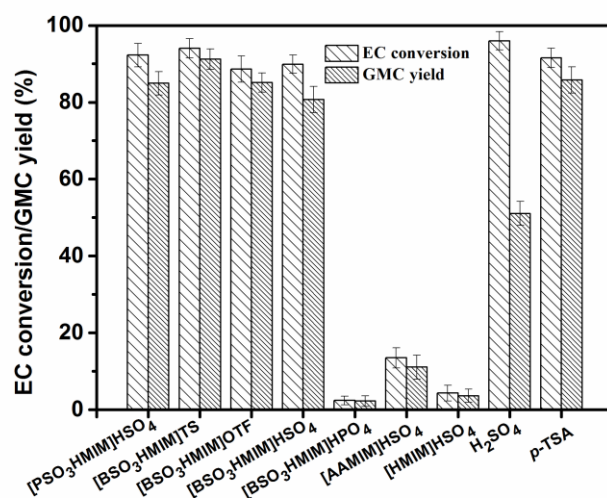
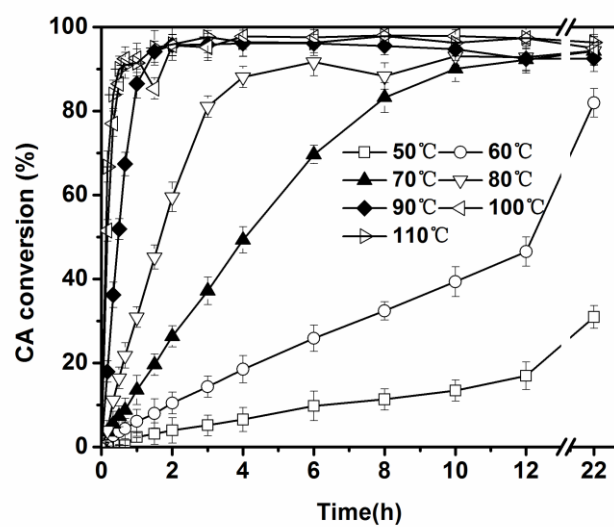
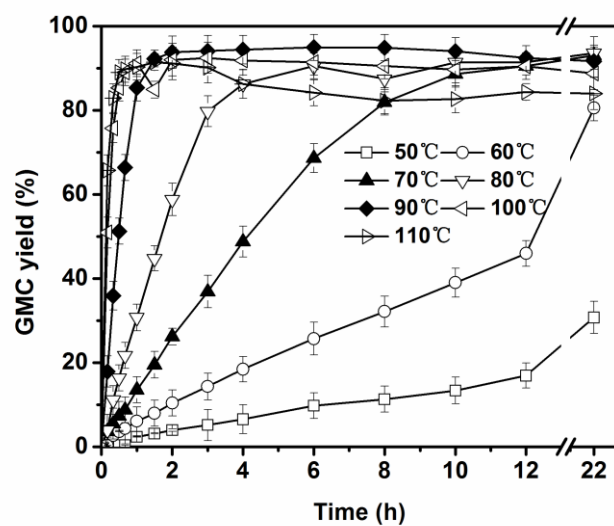


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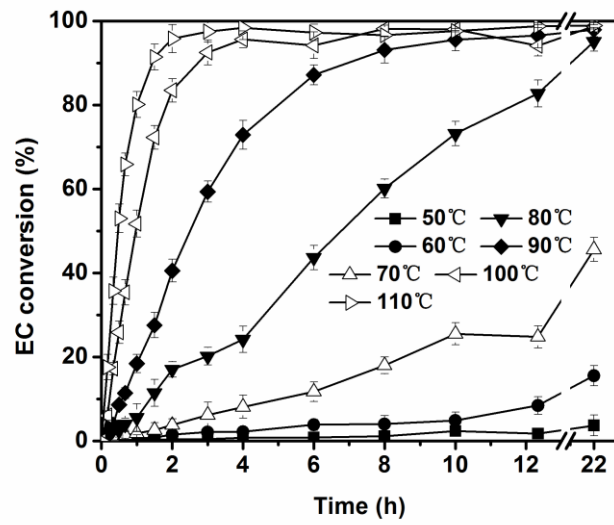
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(B)



(C)



(D)

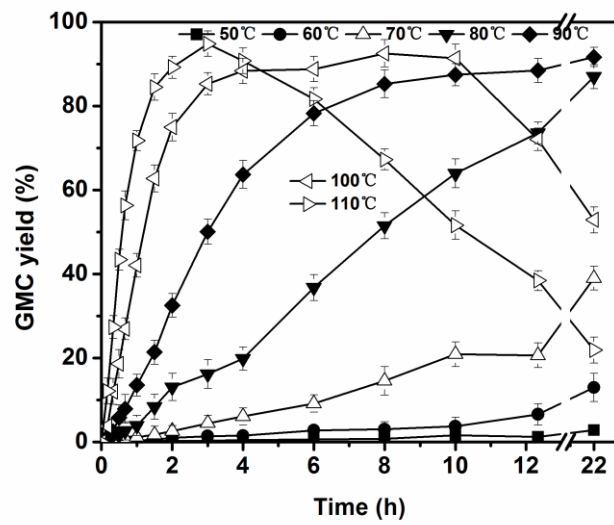
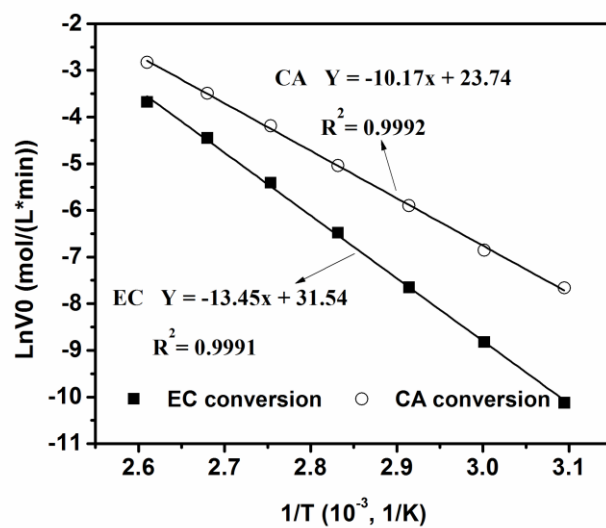


Figure 4

(A)



(B)

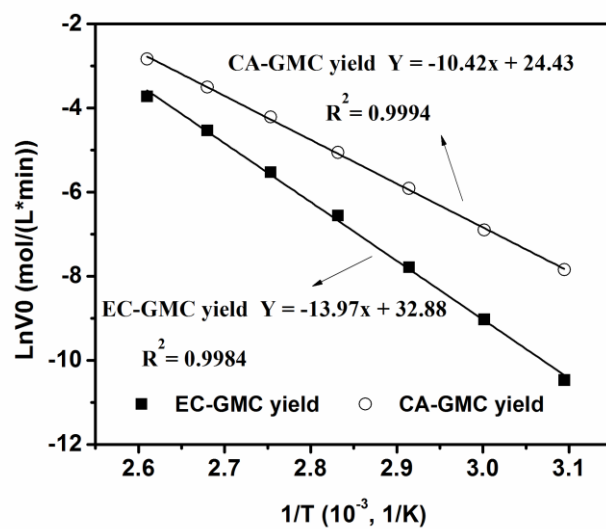
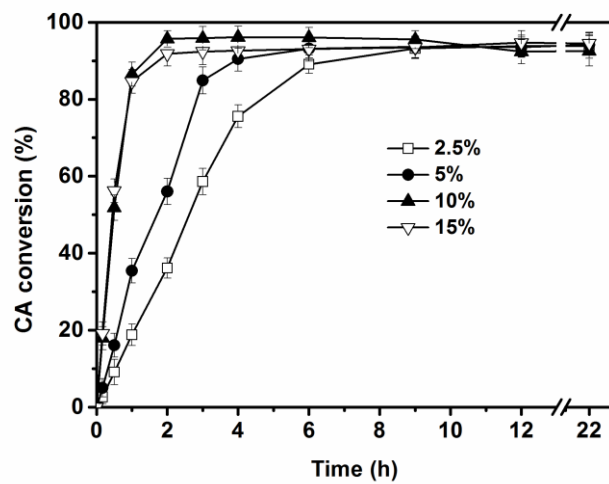
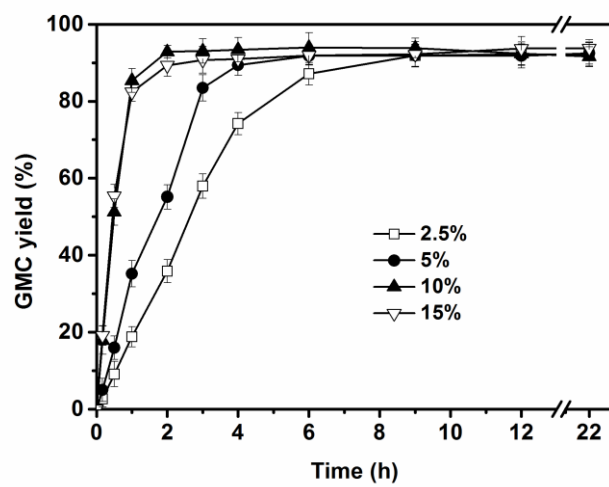


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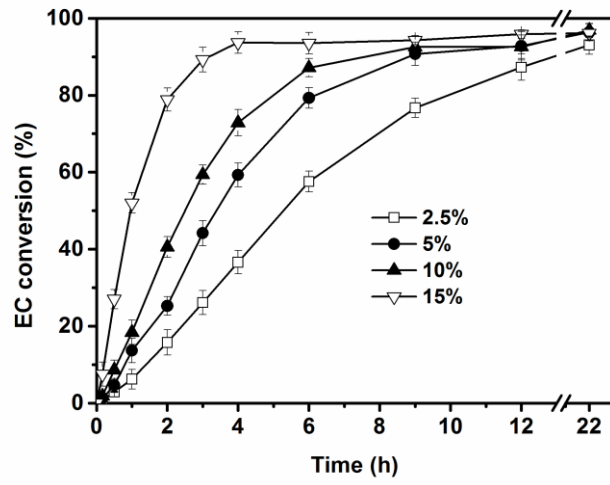
(A)



(B)



(C)



(D)

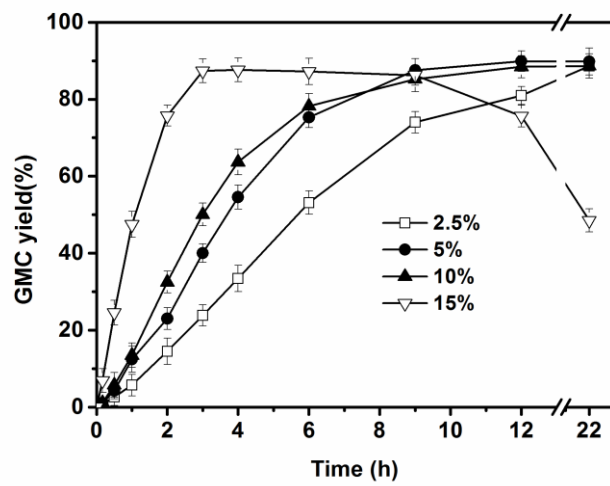
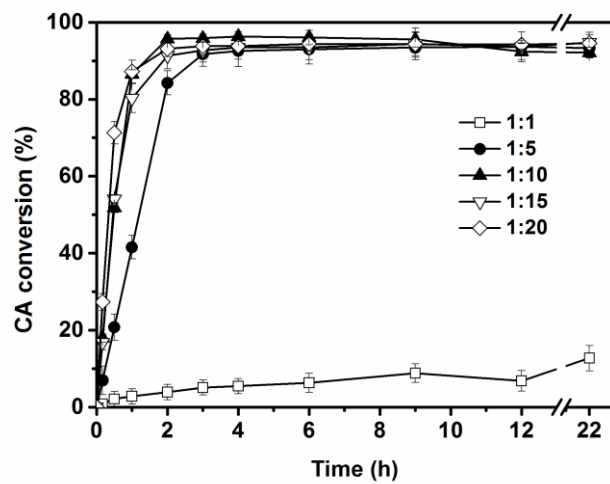
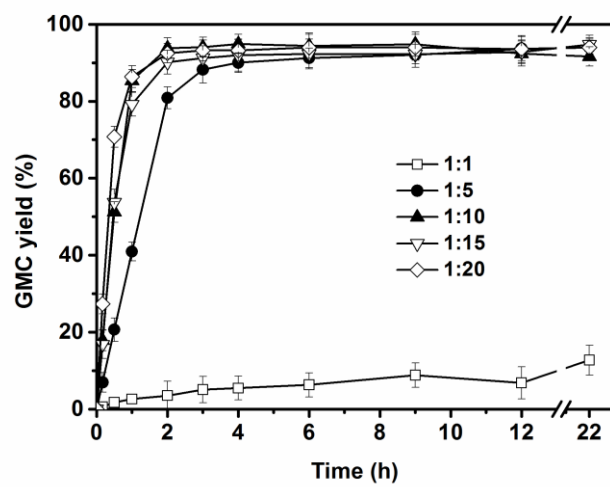


Figure 6

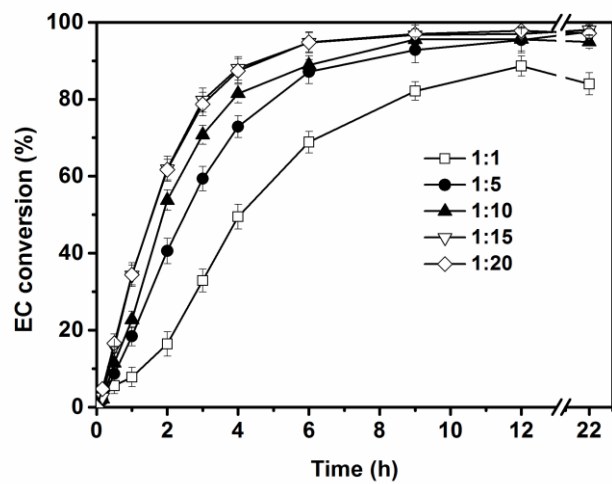
(A)



(B)



(C)



(D)

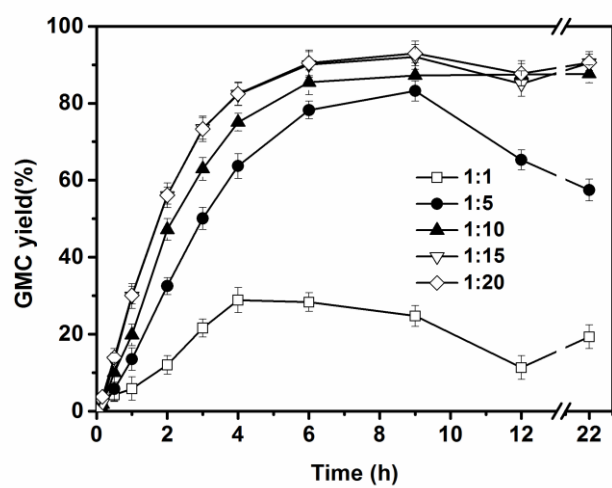
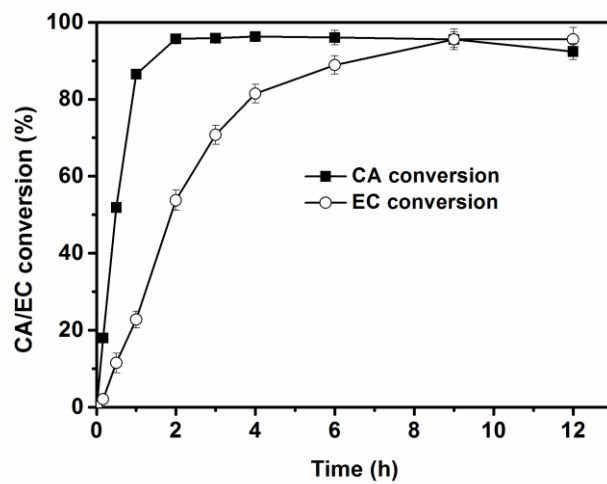


Figure 7

(A)



(B)

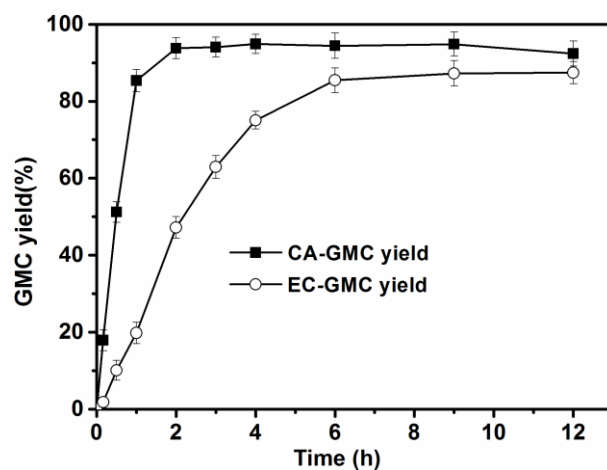
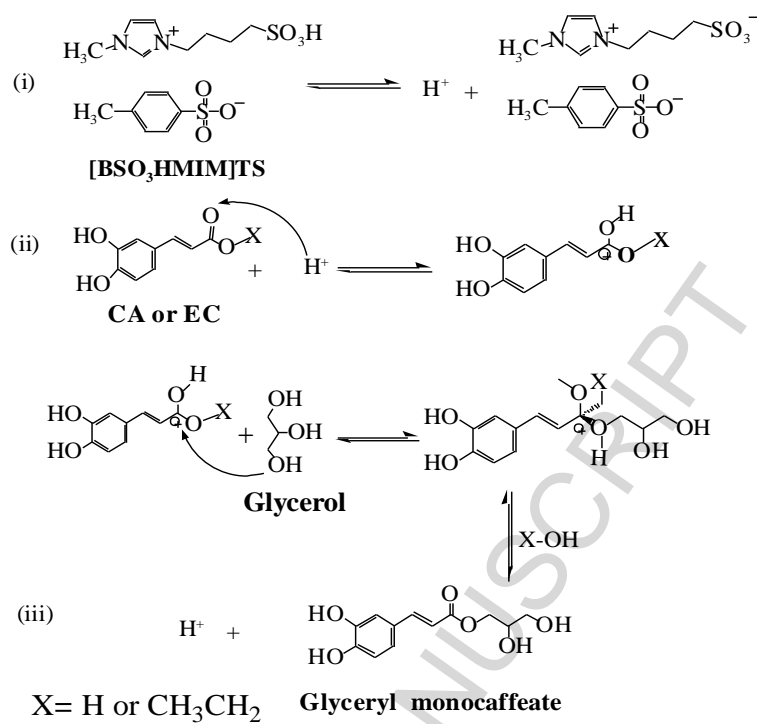
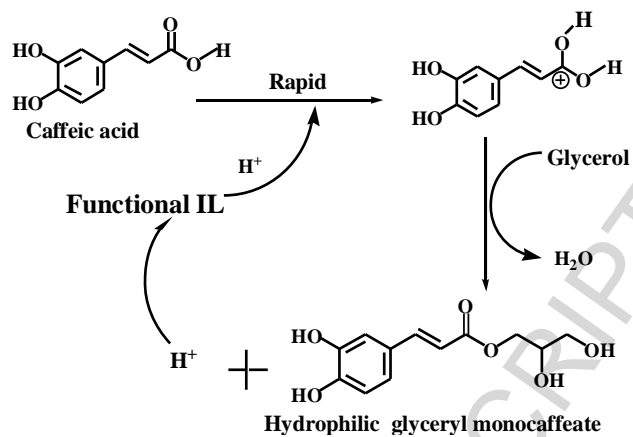


Figure 8



Graphical abstract



Highlights

- 1) Hydrophilic GMC was successfully prepared using ionic liquids as catalysts.
- 2) [BSO₃HMIM]TS showed the best catalytic performance for GMC synthesis.
- 3) Arrhenius equation for GMC formation was $\ln V_0 = 24.433 - 86.67/RT$.
- 4) Activation energies of GMC formation was 86.67 kJ/mol.

ACCEPTED MANUSCRIPT