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**Research Article**

# EFFICIENT SYNTHESIS OF XANTHENE USING A DEEP EUTECTIC SOLVENT CATALYST UNDER SOLVENT-FREE CONDITIONS

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## ABSTRACT

*Several choline chloride–based deep eutectic solvents were synthesized in this study via conventional heating. The obtained catalysts exhibited intermolecular hydrogen bonding, as evidenced by FTIR spectra. In xanthene synthesis, the choline chloride–$FeCl_3$ DES showed the highest catalytic activity; optimal conditions were 80°C, 2 h, and 10 mol% catalyst (relative to benzaldehyde) under solvent-free conditions. Yields decreased for benzaldehyde derivatives bearing substituents compared with unsubstituted benzaldehyde.*

***Keywords:*** choline chloride; Deep eutectic solvent; $FeCl_3$; *para*-toluenesulfonic acid; xanthene

## 1. Introduction

Xanthenes and benzoxanthenes are significant organic compounds. They exhibited diverse pharmacological activities, including anti-inflammatory (Poupelin et al., 1978), antiviral (Ion et al., 1998), antimalarial (Azebaze et al., 2006), and antibacterial (Omolo et al., 2011). Various methods have evolved for the synthesis of xanthene derivatives, which are prepared by the condensation of aromatic aldehydes and β-naphthol with dimedone, using acid catalysts such as the ionic liquid [bmim][$BF_4$] (Fan et al., 2005), $Fe^{3+\text{-montmorillonite}}$ (Song et al., 2007), silica-sulfonic acid (Mohammadi Ziarani et al., 2011), the nano-spherical mesoporous Lewis acid polymer $Sc(OTf)_2$-NSMP (Zhang et al., 2014), $LaCl_3/ClCH_2COOH$ (Pouramiri et al., 2014), nano clinoptilolite (KF/CP NPs) (Balou et al., 2019), nano ZnO (Chhattise et al., 2020), and *L*-proline (Ahmed et al., 2024). In recent years, deep eutectic solvents (DESs) have emerged as an eco-friendly and non-toxic reaction medium due to their unique physicochemical properties, such as negligible vapor pressure, non-toxicity, a relatively wide liquid temperature range, biodegradability, and bio-renewability (Smith et al., 2014). DES is rapidly synthesized through hydrogen bonding interactions between

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hydrogen bond donors, such as succinic acid and malonic acid, and hydrogen bond acceptors, such as choline chloride, a quaternary ammonium salt. Choline chloride-based deep eutectic solvents (DES) have been successfully employed for many condensation reactions (Phadtare et al., 2012), including the benzylation of phenol (Singh et al., 2014), synthesis of spirooxoindole (Azizi et al., 2014), *N*-alkylation of amines (Singh et al., 2011), synthesis of pyrrole and furan (Handy et al., 2014), the Friedländer reaction (Teja et al., 2019), synthesis of hydrazones (Busic et al., 2023), and pyrimidinethione synthesis (Singhal et al., 2025). Herein, we described a synthesis of xanthene derivatives using a choline chloride-based deep eutectic solvent catalyst.

## 2. Experimental

### 2.1. Chemicals and equipment

All chemicals, including choline chloride (99%), iron (III) chloride hexahydrate (99%), *para*-toluenesulfonic acid monohydrate (99%), 5,5-dimethylcyclohexane-1,3-dione (98%), and urea (99%), were supplied by Thermo Scientific. Benzaldehyde (99%), 4-chlorobenzaldehyde (97%), 4-methylbenzaldehyde (97%), and 4-*tert*-butylbenzaldehyde (97%) were obtained from Sigma-Aldrich. Solvents such as *n*-hexane, ethyl acetate, and ethanol were obtained by ChemSol Co. Ltd.

Fourier Transform Infrared (FTIR) spectra were recorded on an ORIGIN JASCO instrument in the range of 400-4000 $cm^{-1}$. The melting point was recorded on a GallenKamp instrument. Nuclear magnetic resonance was recorded on an Avance Bruker 500 MHz spectrometer in DMSO-$d_6$.

### 2.2. Synthesis of deep eutectic solvents

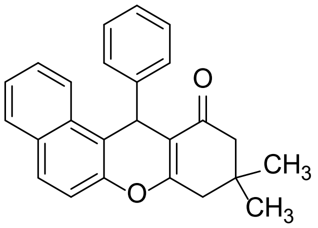
In this work, deep eutectic solvents were synthesized following the procedure described in the previous report (Hu et al., 2015).

A mixture of choline chloride (10 mmol, 1.39 g) and iron (III) chloride hexahydrate (20 mmol, 5.40 g) was heated to 100°C with constant stirring in an oil bath until a clear liquid was observed. The structure of deep eutectic solvent ([ChCl][2$FeCl_3$]) was determined by FTIR methods.

### 2.3. Synthesis of xanthene derivatives

A tube containing a mixture of aromatic aldehydes (1.0 mmol), 5,5-dimethylcyclohexane-1,3-dione (1.0 mmol), β-napthol (1.0 mmol), and the catalyst [ChCl][2$FeCl_3$] (10 mol%) was heated to 80°C for 120 minutes. After completion of the reaction (checked by TLC), 1.0 mL of water was added to the mixture, and it was extracted with ethyl acetate (3 × 5 mL). The ethyl acetate layer was then washed with distilled water (3 × 10 mL) and dried with $Na_2SO_4$. The solvent was removed in a vacuum to obtain the crude product. The purified product was obtained by recrystallization of the crude product in ethanol.

### *2.4. Structure of products*

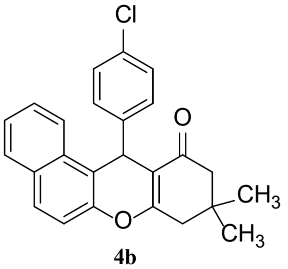


**4a**

White solid, m.p. 151-153°C.

**$^1$H-NMR** (500 MHz, DMSO-*$d_6$*) $\delta_H$ 8.05 (1H, d, *J* = 8.0 Hz), 7.92 (2H, dd, *J* = 3.0 Hz, J = 9.0 Hz), 7.49-7.41 (3H, m), 7.30 (2H, d, *J* = 8.0 Hz), 7.18 (2H, t, *J* = 3.0 Hz, J = 9.0 Hz), 7.05 (1H, t, *J* = 7.5 Hz), 5.58 (1H, s), 2.68 (1H, d, *J* = 17.5 Hz), 2.59 (1H, dd, *J* = 17.5 Hz), 2.34 (1H, d, *J* = 16.0 Hz), 2.14 (1H, d, *J* = 16.0 Hz), 1.06 (3H, s), 0.88 (3H, s) ppm.

**$^{13}$C-NMR** (125 MHz, DMSO-*$d_6$*) $\delta_C$ 196.4, 164.3, 147.6, 145.4, 131.6, 131.1, 129.6, 129.0, 128.6, 128.6, 127.6, 126.7, 125.4, 123.7, 117.8, 117.6, 113.7, 50.6, 40.7, 34.6, 32.4, 29.3, 26.7 ppm.

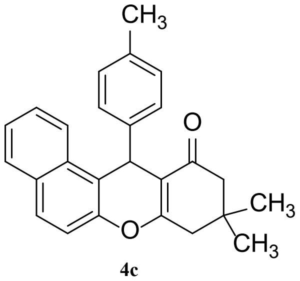


**4b**

White solid, m.p. = 180-182°C.

**$^1$H-NMR** (500 MHz, DMSO-*$d_6$*) $\delta_H$ 8.00 (1H, d, *J* = 8.5 Hz), 7.94-7.91 (2H, m), 7.50-7.44 (3H, m), 7.31 (2H, d, *J* = 6.5 Hz), 7.25 (2H, d, *J* = 6.5 Hz), 5.60 (1H, s), 2.68 (1H, d, *J* = 17.0 Hz), 2.58 (1H, d, *J* = 17.5 Hz), 2.34 (1H, d, *J* = 16.0 Hz), 2.14 (1H, d, *J* = 16.0 Hz), 1.06 (3H, s), 0.88 (3H, s) ppm.

**$^{13}$C-NMR** (125 MHz, DMSO-*$d_6$*) $\delta_C$ 196.4, 164.4, 147.6, 144.3, 131.6, 131.2, 131.0, 130.5, 129.8, 129.1, 128.6, 127.7, 125.5, 123.7, 117.6, 117.2, 113.3, 50.6, 40.7, 34.1, 32.4, 29.3, 26.7 ppm.

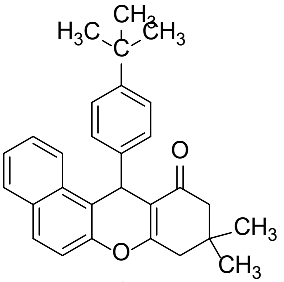


**4c**

White solid, m.p. = 178-179°C.

**$^1$H-NMR** (500 MHz, DMSO-$d_6$) $\delta_H$ 8.04 (1H, d, $J$ = 8.5 Hz), 7.91 (2H, d, $J$ = 9.0 Hz), 7.51-7.43 (3H, m), 7.18 (2H, dd, $J$ = 6.0 Hz), 6.99 (2H, d, $J$ = 7.5 Hz), 5.53 (1H, s), 2.69 (1H, d, $J$ = 17.5 Hz), 2.59 (1H, d, $J$ = 17.5 Hz), 2.34 (1H, d, $J$ = 16.0 Hz), 2.12 (1H, d, $J$ = 16.0 Hz), 2.20 (3H, s), 1.07 (3H, s), 0.89 (3H, s) ppm.

**$^{13}$C-NMR** (125 MHz, DMSO-$d_6$) $\delta_C$ 196.4, 164.1, 147.6, 142.5, 135.7, 131.5, 131.1, 129.5, 129.2, 129.0, 128.5, 127.6, 125.4, 123.8, 117.9, 117.6, 113.8, 50.6, 40.7, 34.2, 32.4, 29.3, 26.7, 21.0 ppm.



**4d**

White solid, m.p. = 208-210°C.

**$^1$H-NMR** (500 MHz, DMSO-$d_6$) $\delta_H$ 8.09 (1H, d, $J$ = 8.5 Hz), 7.91 (2H, dd, $J$ = 3.0 Hz, $J$ = 8.0 Hz), 7.52 (1H, t, $J$ = 7.5 Hz), 7.44 (2H, m), 7.22 (4H, m), 5.55 (1H, s), 2.66 (2H, m), 2.34 (1H, d, $J$ = 16.0 Hz), 2.16 (1H, d, $J$ = 16.0 Hz), 1.16 (9H, s), 1.07 (3H, s), 0.93 (3H, s) ppm.

**$^{13}$C-NMR** (125 MHz, DMSO-$d_6$) $\delta_C$ 196.5, 164.4, 148.8, 147.6, 142.4, 131.5, 131.1, 129.4, 129.0, 128.2, 127.6, 125.4, 125.4, 123.8, 118.0, 117.7, 113.8, 50.6, 40.7, 34.5, 34.0, 32.5, 31.5, 29.1, 27.1 ppm.

## 3. Results and discussion

This study synthesized two deep eutectic solvents using Brønsted acid (*para*-toluenesulfonic acid, PTSA) and Lewis acid ($FeCl_3$) in combination with choline chloride by conventional heating methods. The structures of the prepared deep eutectic solvents were characterized using FTIR spectra, as illustrated in Fig. 1. The FTIR spectrum of the deep eutectic solvent catalyst synthesized from a Brønsted acid (ChCl:PTSA) exhibited differences in comparison to the FTIR spectra of each of the components. The decrease in signal intensity and the broadening of the -OH group vibration at a wavenumber of 3300 cm$^{-1}$ indicated the formation of intermolecular hydrogen bonds between the -OH group of choline chloride and PTSA (Rodriguez et al., 2019). In addition, the FTIR spectrum of the deep eutectic solvent catalyst based on the Lewis acid (ChCl:2$FeCl_3$) showed a shift in the -OH group vibration of choline chloride in the catalyst compared to that of pure choline chloride. The widening and decreasing of the intensity of the -OH group vibration in the catalyst further confirmed the existence of intermolecular hydrogen bonds between choline chloride and $FeCl_3$.

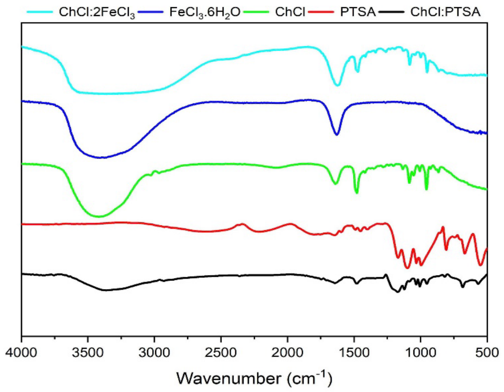
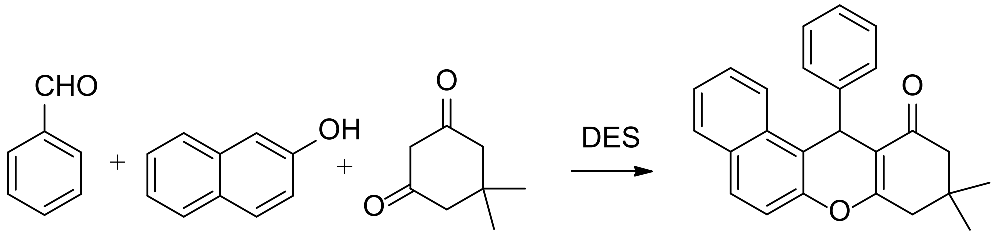


***Figure 1.*** *FTIR spectra of the prepared deep eutectic solvents*

***Table 1.*** *Evaluation of the synthesized deep eutectic solvents in xanthene synthesis*



**1** **2** **3** **4a**

| Entry | Catalyst (mmol) | Time (h) | Temp. (°C) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | [ChCl][$FeCl_3$] (1:2) | 1 | 80 | 66 |
| 2 | [ChCl][PTSA] (1:1) | 1 | 80 | 53 |
| 3 | [ChCl][PTSA][$FeCl_3$] (2:2:1) | 1 | 80 | 43 |
| 4 | [ChCl][Urea][$FeCl_3$] (1:1:1) | 1 | 80 | 0 |

[a] Isolated yield

The research examined the synthesis of four varieties of deep eutectic solvent catalysts based on choline chloride when mixed with Lewis and Brønsted acids, as illustrated in Table 1. In solvent-free conditions, the catalyst consisting of choline chloride and a Lewis acid (Table 1, entry 1) gave better results in xanthene synthesis compared to a Brønsted acid (Table 1, entry 2). The result indicated that Lewis acid activates the carbonyl group of benzaldehyde more efficiently than Brønsted acid. Furthermore, the addition of additional hydrogen bond components in the composition of the deep eutectic solvent, which consists of choline chloride and ferric (III) chloride, resulted in a decreased yield of product **4**. Notably, the addition of urea turned the catalytic effect in the xanthene synthesis reaction ineffective (Table 1, entries 1, 2). Therefore, the catalyst studied for optimizing the reaction conditions was the deep eutectic solvent based on choline chloride and ferric chloride.

***Table 2.*** *Investigation into the conditions for xanthene synthesis reactions*

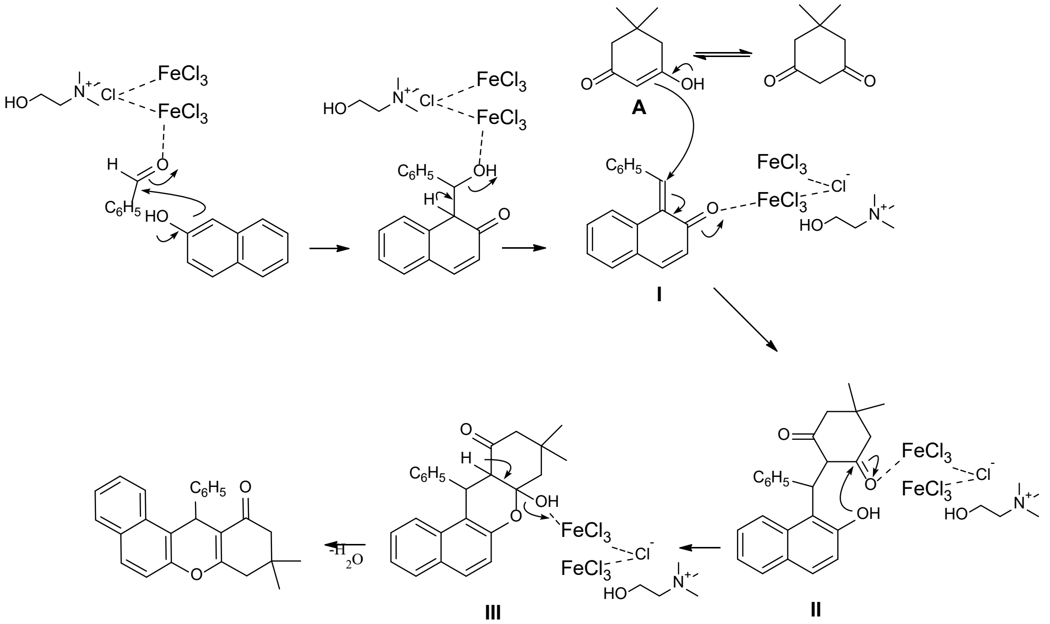
| Entry | Time (h) | Temp. (°C) | Catalyst loading (%mol) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | 1 | 80 | 10 | 66 |
| 2 | 1.5 | 80 | 10 | 69 |
| 3 | 2 | 80 | 10 | 84 |
| 4 | 2.5 | 80 | 10 | 66 |
| 5 | 2 | 70 | 10 | 58 |
| 6 | 2 | 90 | 10 | 45 |
| 7 | 2 | 100 | 10 | 40 |
| 8 | 2 | 80 | 0 | 0 |
| 9 | 2 | 80 | 5 | 43 |
| 10 | 2 | 80 | 12 | 65 |
| 11 | 2 | 80 | 10 | 2[b] |
| 12 | 2 | 80 | 10 | 36[c] |

[a] Isolated yield

[b] Choline chloride as a catalyst

[c] $FeCl_3$ as catalyst

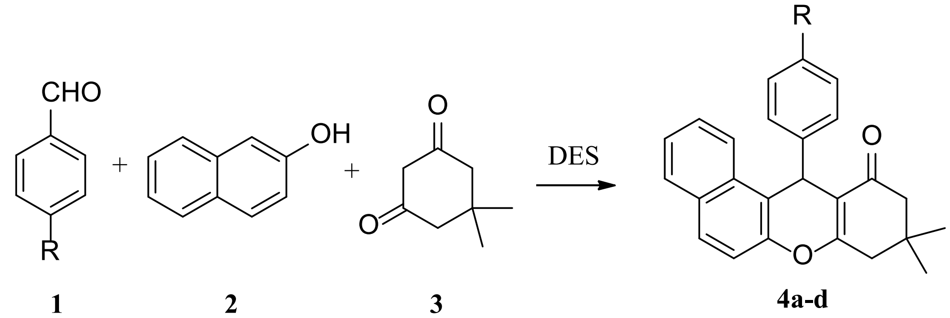
After determining that the deep eutectic solvent catalyst prepared from choline chloride and ferric (III) chloride is the most efficient for xanthene **4** synthesis. The investigated reaction conditions are detailed in Table 2. The optimal reaction time was 2 hours (Table 2, entry 3), and extending the reaction time resulted in a lower yield of product **4** (Table 2, entry 4). The most suitable reaction temperature is 80°C; temperatures below this will slow down the dehydration of intermediate **III** to yield product **4** (Scheme 1), whereas temperatures exceeding 80°C will affect the efficiency of product **4** formation due to substrate change caused by the catalyst at elevated temperatures (Table 2, entries 5, 6, 7). The best conditions for synthesizing product **4** are a temperature of 80°C and a reaction time of 2 hours, conducted under solvent-free conditions. The study also compared the catalyst efficiency with a comparison reaction without a catalyst, which yielded no product **4** (Table 2, entry 8). The ideal catalyst amount for accelerating the reaction was determined to be 10% mol relative to the benzaldehyde substrate (Table 2, entries 9, 10). The investigation indicated that the catalytic performance of individual components of the deep eutectic solvent catalyst, such as choline chloride or ferric (III) chloride, is weaker than that of the synthesized deep eutectic solvent (Table 2, entries 11, 12). These results confirmed the significance of intermolecular hydrogen bonding between choline chloride and ferric (III) chloride in enhancing the catalytic efficiency of ferric (III) chloride.



***Scheme 1.** Proposed mechanism of xanthene synthesis under [ChCl][2FeCl$_3$] catalyst*

The catalyst [ChCl][2FeCl$_3$] activated the carbonyl group of benzaldehyde, leading to β-naphthol to conduct condensation with benzaldehyde, which produced intermediate **I**. In the following step, the dimedone substrate underwent tautomerization catalyzed by [ChCl][2FeCl$_3$], resulting in the formation of enol **A**. The enol **A** subsequently conducted a Michael addition reaction with the carbonyl group of intermediate **I,** activated by the [ChCl][2FeCl$_3$] catalyst, which led to the formation of intermediate **II**. The third step involved a cyclization of the hydroxy group to the activated carbonyl group of intermediate **II**, leading to the formation of intermediate **III**. Finally, intermediate **III** underwent dehydration to yield the product xanthene **4** (Scheme 1).

***Table 3.** Synthesis of xanthene derivatives*



| Entry | R | Product | Yield (%)[a] |
|---|---|---|---|
| 1 | H | **4a** | 84 |
| 2 | Cl | **4b** | 68 |
| 3 | $CH_3$ | **4c** | 54 |
| 4 | $C(CH_3)_3$ | **4d** | 45 |

[a] Isolated yield

Upon determining optimal reaction conditions, benzaldehyde derivatives were changed by using electron-withdrawing (-Cl) and electron-donating (-Me, -*t*-Bu) substituents, as detailed in Table 3. Upon determining optimal reaction conditions, benzaldehyde derivatives were changed by using electron-withdrawing (-Cl) and electron-donating (-Me, -*t*-Bu) substituents, as detailed in Table 3. When the substituent groups on benzaldehyde are changed, the reaction yield falls in the following order: -H (**4a**, 84%) is better than -Cl (**4b**, 68%), $-CH_3$ (**4c**, 54%), $-C(CH_3)_3$, (**4d**, 45%). The maximum yield is achieved in the absence of a substituent group (Table 3, entry 1); the addition of substituent groups (-Cl, $-CH_3$, $-C(CH_3)_3$) lowers the yield compared to the unsubstituted benzaldehyde. Because of the inductive effect, electron-donating groups decreased the density of positive charge on the carbonyl group of benzaldehyde, which decreased the reactivity of the carbonyl group and resulted in a reduced yield of the product. The inductive effect caused electron-withdrawing groups to enhance the density of positive charge on the carbonyl group of benzaldehyde. However, in contrast to benzaldehyde in its liquid form, the state of 4-chlorobenzaldehyde is solid, which resulted in a slower reaction process. This could lower the yield of the final product by influencing the quantity of intermediate I produced in the same duration of time. Electron-withdrawing groups (-Cl) exhibited better results compared to electron-donating groups ($-CH_3$, $-C(CH_3)_3$). The *tert*-butyl group lowered the reactivity of the carbonyl group more significantly than the methyl group, hence decreasing the yield of xanthene synthesis.

***Table 4.*** *Comparing the prepared catalyst with other catalysts*

| Entry | Catalyst, condition | Time (min.) | Yield (%) | Reference |
|---|---|---|---|---|
| 1 | $[ChCl][2FeCl_3]$, 80°C, solvent-free | 120 | 84 | This work |
| 2 | PTSA, 80°C, $[bmim]BF_4$ | 180 | 90 | Khurana et al., 2009 |
| 3 | KF/CP NPS, 80°C, solvent-free | 60 | 88 | Balou et al., 2019 |
| 4 | DABCO/Amberlyst-15, 120°C, solvent-free | 120 | 92 | Bosica et al., 2023 |
| 5 | Sulfonated fructose, EtOH-$H_2O$, reflux | 35 | 89 | Kakeshpour et al., 2024 |

When compared to other published studies, the research results in this study showed that the synthesized catalyst is equally effective. The reaction required high temperatures for a long time. The reaction time is reduced when the reaction is conducted at higher temperatures.

## 4. Conclusion

The study developed deep eutectic solvents using choline chloride and Lewis and Bronsted acids, with the Lewis acid catalyst superior to the Bronsted acid in the xanthene synthesis reaction. Furthermore, adding a hydrogen bond component into the $[ChCl][2FeCl_3]$ catalyst significantly lowered its catalytic activity due to competitive hydrogen bond formation. This result illustrated the effectiveness of $FeCl_3$ in enhancing catalytic activity in the formation of hydrogen bonds with choline chloride. The optimal conditions for the xanthene synthesis reaction were examined, including a reaction temperature of 80°C, a reaction time of two hours, and a catalyst loading of 10% mol compared to the benzaldehyde substrate. Furthermore, various benzaldehyde derivatives were examined and employed to synthesize xanthene derivatives, revealing that bulky substituents significantly lowered the efficiency of the synthesis.

❖ ***Conflict of Interest:*** *Authors have no conflict of interest to declare.*

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# TỔNG HỢP HIỆU QUẢ XANTHENE SỬ DỤNG DEEP EUTECTIC SOLVENT TRONG ĐIỀU KIỆN KHÔNG DUNG MÔI

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## TÓM TẮT

*Bài báo nghiên cứu tổng hợp một số deep eutectic solvents dựa trên choline chloride sử dụng phương pháp đun nóng truyền thống. Các xúc tác điều chế được xác định sự hình thành liên kết hydrogen liên phân tử dựa trên phổ FTIR. Kết quả so sánh hiệu quả xúc tác trên phản ứng tổng hợp xanthene cho thấy xúc tác điều chế từ choline chloride và $FeCl_3$ có hiệu quả tốt nhất với điều kiện thực hiện phản ứng tối ưu là nhiệt độ 80 °C, thời gian phản ứng 2h và lượng xúc tác sử dụng 10% mol so với benzaldehyde trong điều kiện không dung môi. Khi thay đổi dẫn xuất của benzaldehyde mang các nhóm thế khác nhau thì hiệu suất tổng hợp dẫn xuất xanthene thấp hơn so với khi benzaldehyde không mang nhóm thế.*

***Từ khóa:*** choline chloride; Deep eutectic solvent; $FeCl_3$; *para*-toluenesulfonic acid; xanthene