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A novel acidic deep eutectic solvent for sustainable and efficient coumarin synthesis

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A novel acidic deep eutectic solvent (ADES) has been developed as an efficient and sustainable alternative to traditional solvents and catalysts in organic synthesis. The ADES was synthesized through a simple one-pot procedure involving benzyl chloride, 2-(dimethylamino)ethanol, and *p*-toluenesulfonic acid, yielding a homogeneous liquid. Structural and compositional characterization was performed using FTIR and NMR spectroscopy. The catalytic performance of the synthesized ADES was evaluated in the Pechmann condensation for the synthesis of coumarins. The reaction proceeded under mild conditions using commercially available starting materials, with reaction times ranging from 5 to 200 min and isolated yields between 72% and 97%. The process is operationally simple and readily scalable, indicating its suitability for industrial implementation. Importantly, the ADES demonstrated excellent recyclability, maintaining catalytic activity over five consecutive cycles without significant loss of efficiency which makes it an environmentally friendly and economically viable option for large-scale synthesis.

Keywords Acidic deep eutectic solvent, Sustainable catalysis, Coumarin synthesis, Green chemistry, Recyclable solvent system

Deep eutectic solvents (DESs) are an emerging class of environmentally benign solvents formed by combining a hydrogen bond acceptor (HBA), such as choline chloride or metal salts, to a hydrogen bond donor (HBD), including organic acids, sugars, or urea. This combination results in a eutectic mixture to a melting point significantly lower than that of the individual components, primarily due to strong hydrogen bonding interactions between the constituents[1,2]. The synthesis of DESs is straightforward, typically involving gentle heating and mixing until a homogeneous liquid forms[3]. Structurally, DESs exhibit disrupted crystalline lattices, imparting distinctive solvation properties and enabling tunable physicochemical characteristics[4,5]. Since their initial introduction by Abbott et al. in 2003, DESs have attracted considerable interest across a wide range of applications, including catalysis, metal extraction, electrochemistry, biomass processing, and pharmaceutical formulations[6-9]. Their low toxicity, biodegradability, ease of preparation, and capacity to dissolve a broad array of compounds, make them attractive alternatives to conventional solvents[10-15]. A subset of DESs, known as acidic deep eutectic solvents (ADESs), are specifically tailored to function as acidic media. These are formed by combining HBAs such as choline chloride or metal salts with acidic HBDs, including organic acids like oxalic acid, citric acid, formic acid, lactic acid, or p-toluenesulfonic acid[16-18]. The resulting ADESs feature strong hydrogen bonding networks, tunable acidity, and high solubility for polar substrates. These characteristics render them especially useful in acid-catalyzed transformations, metal processing techniques and green chemistry applications such as CO_2 capture and environmental remediation[19-23].

Coumarin is an aromatic organic compound found abundantly in various plant sources such as sweet clover, cinnamon, lavender, and tonka beans[24–28]. Coumarin is characterized by a sweet odor and serves as the structural core for numerous bioactive derivatives[29-32]. These derivatives such as warfarin, dicoumarol, scopoletin, umbelliferone, and aesculetin exhibit a wide range of pharmacological activities including anticoagulant, antioxidant, anti-inflammatory, antibacterial, and anticancer effects (Fig. 1)[33–35].In addition to pharmaceutical applications, coumarins are also utilized in the fragrance and cosmetics industries[36]. Over the years, several synthetic strategies have been developed for the preparation of coumarin derivatives, including the Pechmann condensation, Knoevenagel condensation, and Wittig reaction[37-43]. Recent research has increasingly focused on green chemistry approaches, such as the use of DESs, ionic liquids, and microwave-assisted synthesis, to enhance sustainability and reduce environmental impact. Notably, a DES system based on choline chloride and L-(+)-tartaric acid has been previously applied in the Pechmann condensation for coumarin synthesis[44]. While

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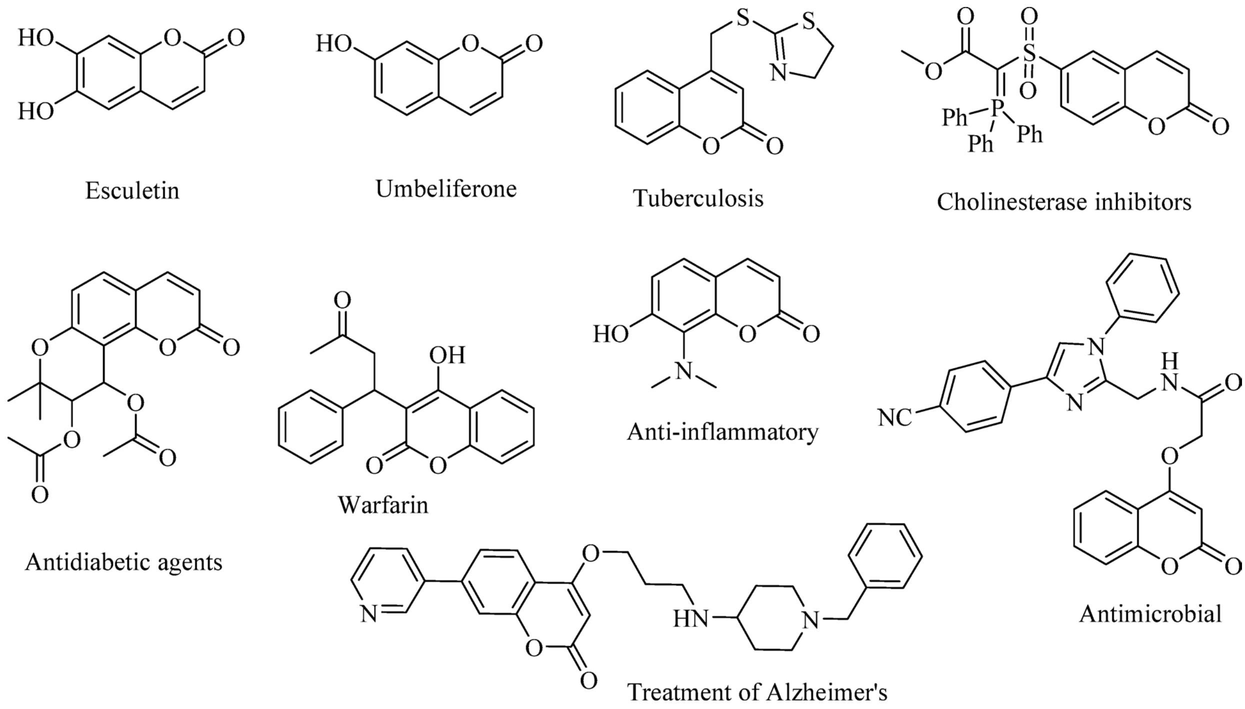


Fig. 1. Industrial applications of coumarin derivatives.

effective, this approach required relatively large quantities of DES, extended reaction times, and harsher reaction conditions, thereby limiting its scalability and practical utility.

In recent years, our research is focused on advancing the principles of green chemistry in organic synthesis through the development of sustainable methodologies, including aqueous systems, solvent-free conditions, and DESs[45-47]. In this context, we have designed and synthesized a novel acidic deep eutectic solvent (ADES), composed of benzyl chloride, 2-(dimethylamino)ethanol, and *p*-toluenesulfonic acid. The synthesized ADES was characterized using various spectroscopic techniques, which confirms its composition and structure. This novel ADES serves as an effective and versatile catalytic medium, facilitating the construction of structurally diverse coumarin frameworks employing various substituted phenols and salicylaldehyde in combination with different β-ketoesters.

The experimental

Materials and methods

All reagents, including phenol derivatives, salicylaldehydes, β-keto esters, benzyl chloride, 2-(dimethylamino) ethanol, and p-toluenesulfonic acid, were purchased from Sigma-Aldrich and used without further purification. Melting points were determined using a Büchi 535 melting point apparatus. Fourier-transform infrared (FT-IR) spectra were recorded on an AVATAR spectrometer. Nuclear magnetic resonance (NMR) spectra of ADES were recorded in DMSO-d6 using a Bruker Fourier 300 MHz spectrometer (Germany).

Preparation of ADES

A mixture of benzyl chloride (200 mmol) and 2-(dimethylamino)ethanol (200 mmol) was placed in a round-bottom flask equipped with a magnetic stirrer and heated to 80 °C under a nitrogen atmosphere. The reaction mixture was stirred continuously for 8 h. Upon completion of the initial stage, *p*-toluenesulfonic acid (200 mmol) was added to the reaction mixture and stirring was continued at the same temperature for an additional 2 h. The reaction mixture gradually transformed into a viscous liquid, indicating the successful formation of the acidic deep eutectic solvent (ADES), with a viscosity of 680 cP, density of 1.26 g/mL, and a pH of 2.3 (100 mM solution, 25 °C). (Fig. 2).

Typical procedure for preparation of 7-hydroxy-4-methylcoumarin derivatives

In a typical experiment, resorcinol (1.0 mmol) and ethyl acetoacetate (1.0 mmol) were dissolved in the synthesized ADES (0.5 mL) in a test tube equipped with a magnetic stir bar and sealed with a septum. The reaction mixture was stirred vigorously at 100 °C for 80–200 min. Upon completion, the mixture was allowed to cool to room temperature, followed by the addition of distilled water (15 mL). The resulting precipitate was isolated by centrifugation and purified either by recrystallization from ethanol or tetrahydrofuran, or by column chromatography using a petroleum ether/ethyl acetate mixture as the eluent, affording pure 7-hydroxy-4-methylcoumarin derivatives. All synthesized compounds were previously reported in the literature. Their identities were confirmed by comparison of melting points with those of authentic samples or previously published data.

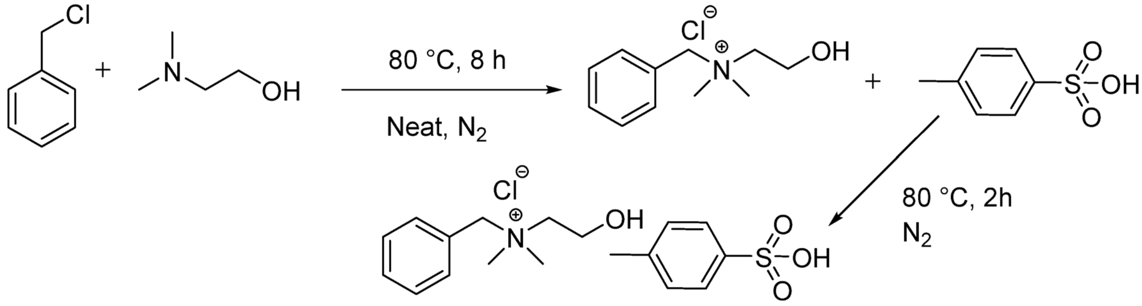


Fig. 2. Preparation of ADES.

Typical procedure for the preparation of 3-ethoxycarbonylcoumarin derivatives

In a test tube with magnetic stirring bar, a mixture of salicylaldehyde (1.0 mmol) and dimethyl malonate (1.0 mmol) was added to water (5 mL) containing DES (0.2 mL), and the reaction mixture was stirred vigorously at room temperature for 5–15 min. Upon completion of the reaction, the resulting crystalline product was isolated by simple filtration to afford 3-ethoxycarbonylcoumarin. The crude solid obtained was further purified by recrystallization from ethanol to give the pure product. All synthesized compounds were crystalline, and their melting points were determined and compared with those reported in the literature, confirming their identity and purity.

Results and discussion

Characterizations

Characterization of ADES by NMR and FTIR analysis

After the preparation of ADES, characterization was carried out using ^{1}H NMR and FTIR spectroscopy. In the ^{1}H NMR spectrum recorded in DMSO-d$_6$ solvent, the methyl protons of p-toluenesulfonic acid (PTSA) appeared as a singlet at 2.29 ppm. The methylene group (CH_2) attached to the hydroxyl group (–OH) was observed at 3.01 ppm. The CH_2 and CH_3 groups attached to the nitrogen atom (–N) appeared at 3.39 ppm and 3.91 ppm, respectively. The benzylic CH_2 protons were found at 4.59 ppm. The aromatic protons corresponding to both phenyl rings were detected in the range of 7.12–7.59 ppm (Fig. 3).

Furthermore, the ^{13}C NMR spectrum of ADES confirmed the structure of the synthesized ADES. The methyl carbon of *p*-toluenesulfonic acid was observed at 21.2 ppm. The methylene carbon (CH_2) attached to the hydroxyl group appeared at 50.2 ppm. The methyl groups attached to the nitrogen atom were detected at 55.3 ppm, while the methylene carbon attached to the nitrogen was observed at 65.3 ppm. The benzylic methylene carbon (CH_2–Ph) was found at 67.9 ppm. Finally, the aromatic carbons for both phenyl rings were observed in the range of 125.9–145.8 ppm (Fig. 4).

The chemical structures of the ADES system were further analyzed based on FT-IR spectroscopy. As shown in Fig. 5, ADES exhibited a broad absorption peak around 3362 cm^{-1}, which corresponds to the O–H stretching vibration, indicating the presence of hydroxyl groups in the ADES structure as well as absorbed moisture from the environment. A broad peak observed at approximately 2123 cm^{-1} is attributed to strong interactions between the salt and p-toluenesulfonic acid. Additional characteristic peaks were observed at 1637 cm^{-1} and 1481 cm^{-1}, corresponding to the bending vibration and stretching vibration of the N–C bond in the amino group, respectively. The peak at 860 cm^{-1} is ascribed to the stretching vibration of the S–OH group. Furthermore, two distinct peaks at 1085 cm^{-1} and 1217 cm^{-1} were assigned to the antisymmetric and symmetric stretching vibrations of the S = O bonds, respectively.

Catalytic evaluation of DES in the synthesis of coumarin derivatives

Following the preparation and characterization of ADES composed of p-toluenesulfonic acid (PTSA) and benzyl dimethyl (2-hydroxyethyl) ammonium chloride (BDC), their catalytic activity was evaluated in the synthesis of coumarin derivatives. The reaction between resorcinol (1.0 mmol) and ethyl acetoacetate (1.0 mmol) served as a model, and various DES systems and conditions were screened. The results are summarized in Table 1. Among the DES system tested, the PTSA–BDC system demonstrated the highest catalytic efficiency, yielding the target coumarin derivative **3a** in excellent yield. First, the model reaction was carried out at room temperature for 200 min, resulting in negligible product formation. (Table 1, Entry 1). To improve the reaction yield, elevated temperatures were investigated. Although a slightly higher yield was obtained at 120 °C compared to 100 °C, the difference was not significant. Consequently, 100 °C was selected as the optimal reaction temperature for subsequent experiments (Table 1, Entry 5). To further evaluate the catalytic potential of alternative DES systems, the model reaction was carried out under optimized conditions (100 °C, 120 min) using various DES combinations, including oxalic acid: BDC (Entry 7), $SnCl_2$:BDC (Entry 8), $ZnCl_2$:BDC (Entry 9), $SnCl_2$–ChCl (Entry 10), $ZnCl_2$–ChCl (Entry 11), PTSA–ChCl (Entry 12), oxalic acid–ChCl (Entry 13), and urea–ChCl (Entry 14). However, none of these systems outperformed the PTSA–BDC combination in terms of product yield, thereby confirming its superior catalytic efficiency.

[a] Isolated yields. *ChCl* choline chloride, *BDC* benzyl dimethyl (2-hydroxyethyl) ammonium chloride, *OX* Oxalic acid.

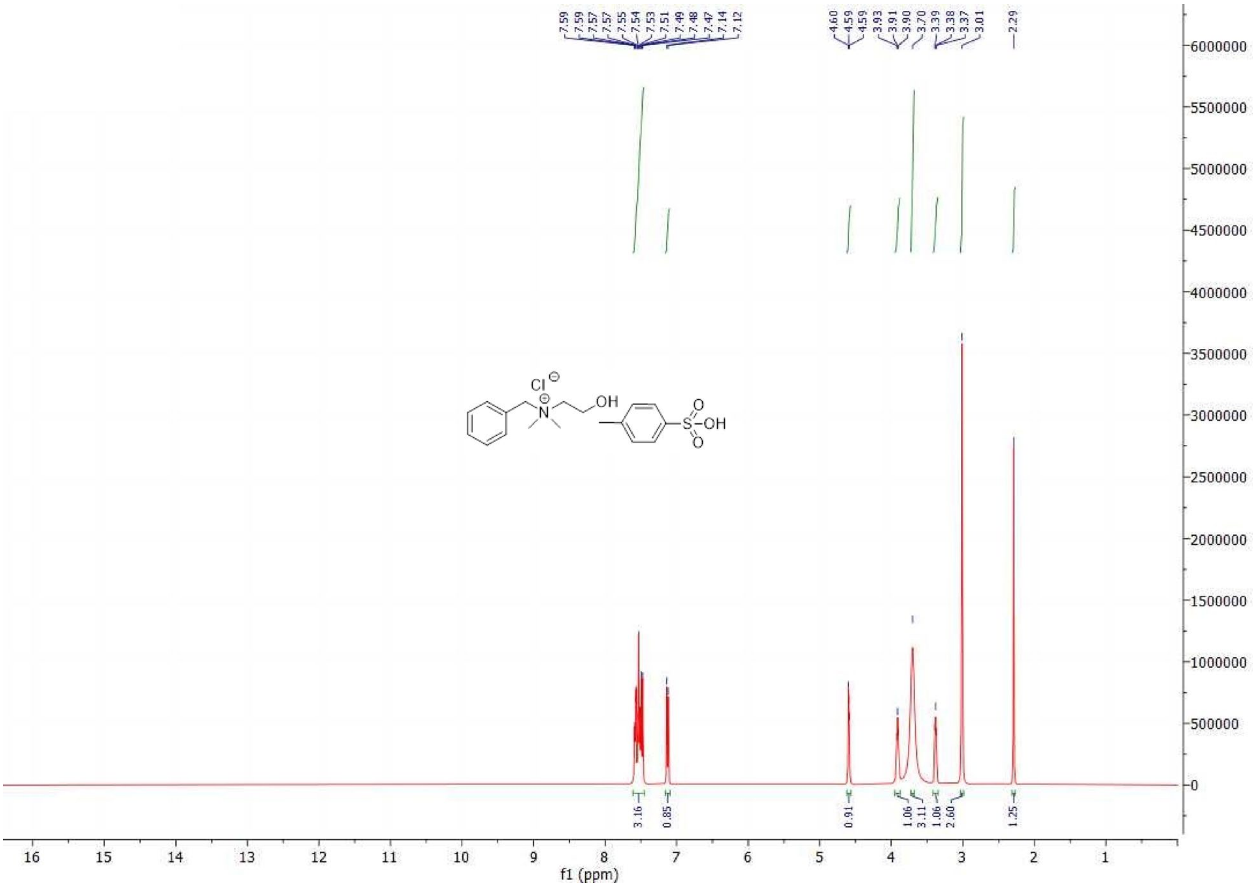


Fig. 3. ^{1}H NMR spectra of ADES.

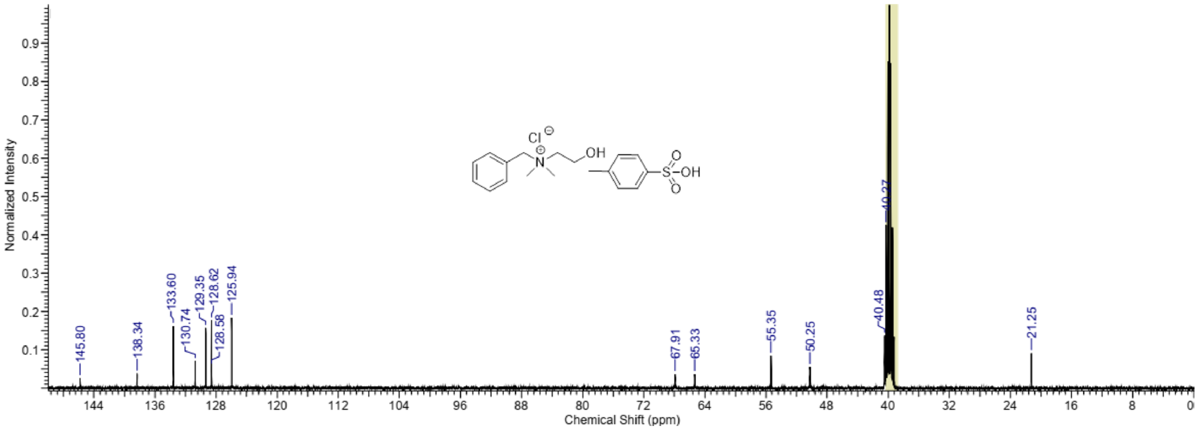


Fig. 4. ^{13}C NMR spectra of ADES.

Under the optimized reaction conditions, the scope of the reaction was extended to various phenols and β-ketoester derivatives, and the results summarized in Table 2. This environmentally benign procedure provides an efficient and general approach to the synthesis of coumarin derivatives, accommodating a wide range of functional groups including chloro, methoxy, methyl, and hydroxy on the phenolic ring. Both ortho-, meta-, and para-substituted phenols successfully underwent the Pechmann condensation, reacting smoothly with different β-ketoesters under operationally simple and mild conditions. The method proved to be broadly applicable, furnishing a diverse set of substituted coumarins in good to excellent yields, thereby demonstrating the versatility and efficiency of the PTSA/BDC based DES catalytic system[48].

To further evaluate the reliability and versatility of the developed DES catalytic system, the scope of the reaction was extended to include salicylaldehyde and β-ketoester derivatives. As a model reaction, salicylaldehyde

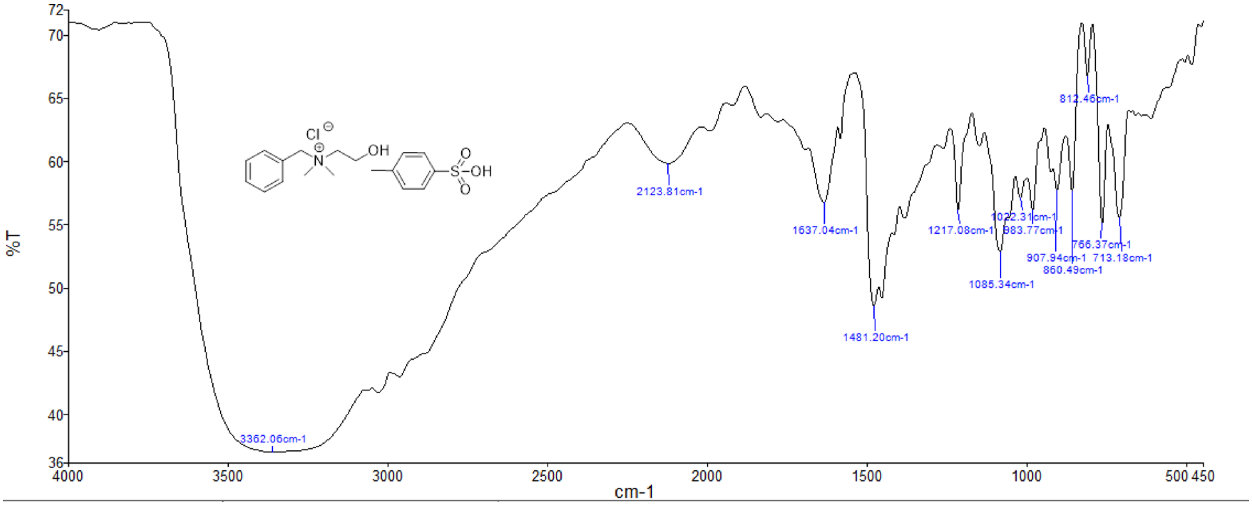
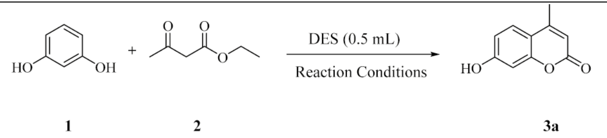


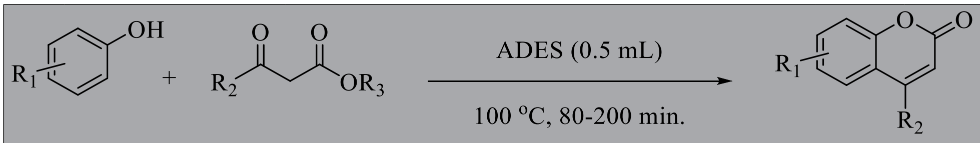
Fig. 5. FTIR analysis of ADES.



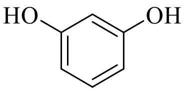
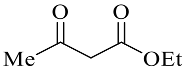
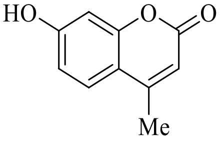
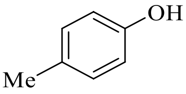
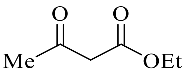
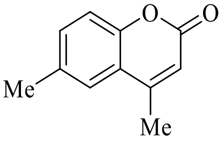
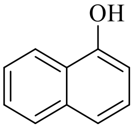
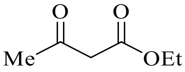
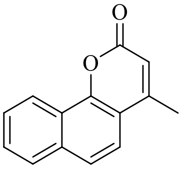
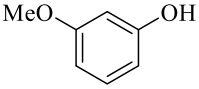
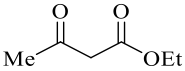
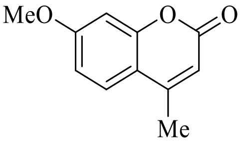
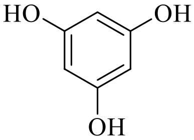
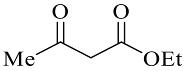
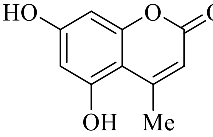
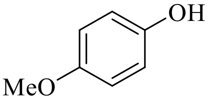
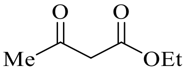
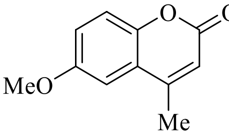
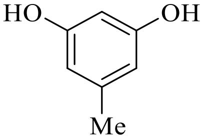
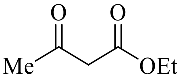
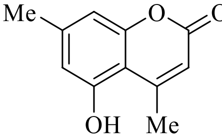
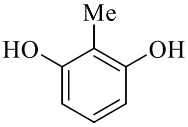
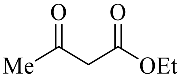
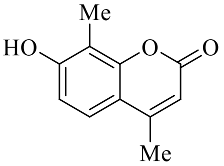
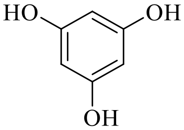
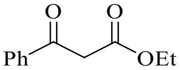
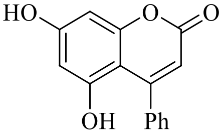
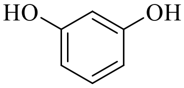
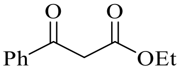
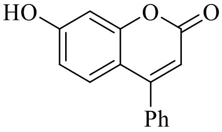
Entry	DES (0.5 mL)	Temp. (ºC)	Time (min.)	Yield (%)[a]
1	PTSA:BDC (1:1)	25	200	Trace
2	PTSA:BDC (1:1)	40	200	Trace
3	PTSA:BDC (1:1)	60	200	45
4	PTSA:BDC (1:1)	80	200	68
5	PTSA:BDC (1:1)	100	120	92
6	PTSA:BDC (1:1)	120	120	92
7	Ox:BDC (1:1)	100	120	62
8	$SnCl_2$:BDC (2:1)	100	120	67
9	$ZnCl_2$:BDC (2:1)	100	120	73
10	$SnCl_2$:ChCl (2:1)	100	120	76
11	$ZnCl_2$:ChCl (2:1)	100	120	45
12	PTSA:ChCl (2:1)	100	120	57
13	OX:ChCl (2:1)	100	120	41
14	Urea:ChCl (2:1)	100	120	Trace

Table 1. Products of salicylaldehyde and ketoesters in coumarin Synthesis.

(1.0 mmol) and dimethyl malonate (1.0 mmol) were selected for the synthesis of 3-ethoxycarbonylcoumarin (**6a**). In the initial attempt, the reaction was performed in the PTSA–BDC-based DES system (Table 3, Entry 1) and this system afforded negligible yields. Consequently, a series of experiments were conducted under varied reaction conditions using different DES systems. The results of these screening experiments are summarized in Table 3. Following extensive trial-and-error optimization, it was discovered that the Knoevenagel condensation of salicylaldehyde (**4**) and diethyl malonate (**5**) proceeded efficiently and rapidly in water in the presence of DES at room temperature. The screening of various deep eutectic solvents (DESs) in aqueous media for the Pechmann condensation reaction revealed that a piperidine/acetic acid-based DES was the most effective, offering excellent product yield and cost-efficiency under room temperature (Table 3, entry 15). Interestingly, further increasing the amount of DES, prolonging the reaction time, or elevating the temperature to 60 °C did not result in any noticeable improvement in yield, highlighting the efficiency of the optimized conditions. In an effort to identify the most suitable reaction medium, several solvents were examined, including choline chloride–urea DES, polyethylene glycol (PEG), tetrahydrofuran (THF), dichloromethane (DCM), and ethanol. Among these, water was found to be the most effective solvent, significantly enhancing the yield of the desired coumarin derivatives under mild and environmentally friendly conditions. This observation is strongly supported by the experimental



1 **2** **3**

Entry	Phenol	β-Ketoester	Product	Yield [%]	Mp (°C)	
					Found	Reported
1			 **3a**	92	183–185	185-187[42]
2			 **3b**	82	149–151	150-151[42]
3			 **3c**	72	154–155	155-157[40]
4			 **3d**	92	161–162	160-162[42]
5			 **3e**	95	280–282	281-282[48]
6			 **3f**	76	159–161	162-163[26]
7			 **3g**	80	245–247	244-246[41]
8			 **3h**	95	215–217	217-218[42]
9			 **3i**	97	279–283	280-285[44]
10			 **3j**	89	242–244	240-244[41]

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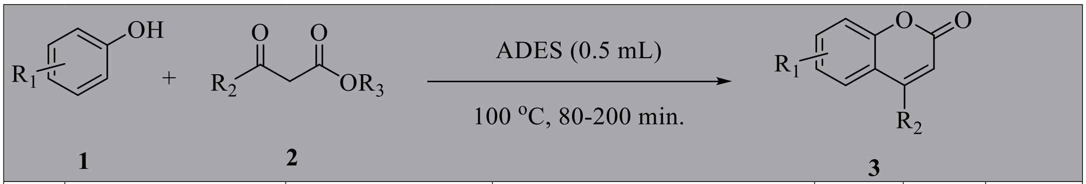


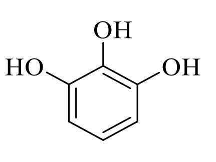
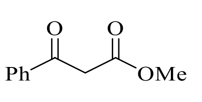
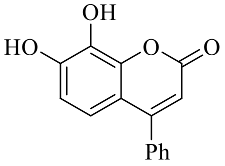
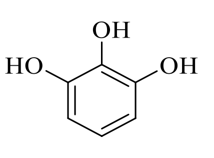
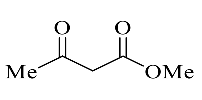
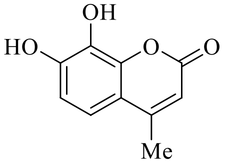
11			 **3k**	84	234–236	235-236[34]
12			 **3l**	95	240–241	242-244[37]

Table 2. Pechmann reactions in ADES under optimized condition.

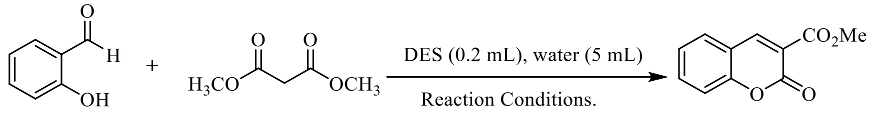
data presented in Table 3 confirming the advantage of using water as the reaction medium in combination with the piperidine/acetic acid DES system.

Under the optimized reaction conditions, various salicylaldehyde and ketoester derivatives were subjected to the optimized DES system, and the results are summarized in Table 4. The piperidine/acetic acid-based DES proved to be highly effective for all tested starting materials, showing excellent reactivity. A variety of salicylaldehyde derivatives, including 5-bromosalicylaldehyde and 4-hydroxy salicylaldehyde, along with ketoesters such as ethyl acetoacetate, methyl acetoacetate, malonitrile, and phenylacetoacetate, were successfully converted their corresponding coumarin products with good to excellent yields. The reactions proceeded rapidly, typically completing in less than 15 min, with clean formation of the desired products. Notably, the reaction system allowed for easy isolation of the products, with the precipitated coumarins being formed upon addition of additional water at the reaction mixture. This approach minimized the need for volatile organic solvents in the workup process. In many cases, purification was unnecessary, as the products obtained after direct filtration of the precipitate were reasonably pure. Importantly, compound **6a** was synthesized on a larger scale (5 g, 97% yield) in just 10 min under similar conditions, demonstrating the scalability and efficiency of the method.

The reusability of the DES system was thoroughly investigated for the synthesis of compound **6a** in a model reaction. The results revealed that the DES system remained highly effective over five consecutive reaction cycles without any significant decrease in yield. After each reaction, the solid product was separated by centrifugation, and the aqueous phase containing the DES was directly reused in the subsequent run. Figure 6 illustrates the stability of the system, with yields remaining consistent across all five cycles. This demonstrates the high catalytic efficiency and recyclability of the DES, which key advantage for large-scale industrial applications, aligning with the principles of green chemistry by minimizing waste and solvent use while maintaining excellent performance.

Conclusion

In summary, this study explored the use of novel acidic deep eutectic solvents as both catalysts and reaction media for the synthesis of coumarin under mild conditions. The ADES developed in this study offers several significant advantages over traditional solvents and catalysts. It provides a sustainable, environmentally friendly alternative by eliminating the need for hazardous reagents while maintaining high catalytic efficiency. The ADES system enables coumarin synthesis under mild conditions, thereby reducing energy consumption and minimizing waste generation. Moreover, the solvent demonstrated excellent recyclability, maintaining its catalytic activity for at least five consecutive runs with no significant loss in performance, making it both cost-effective and suitable for industrial-scale applications. Its dual function as both solvent and catalyst further simplifies the reaction system, enhancing the overall efficiency of the process.



4 **5** **6a**

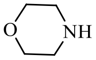
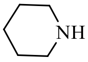
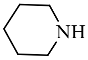
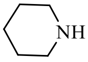
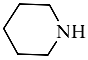
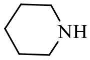
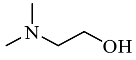
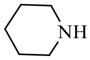
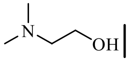
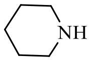
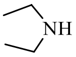
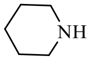
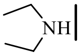
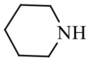
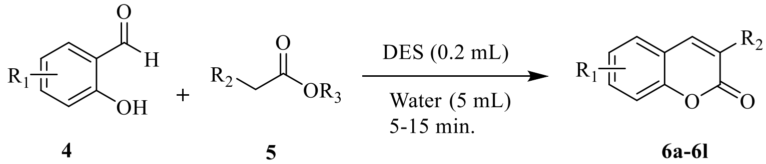
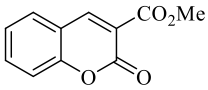
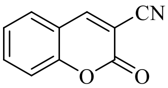
Entry	DES (1.0 mL)	Yields (%)^a	Entry	DES (1.0 mL)	Yields (%)^a
1	PTSA:BDC (1:1)	45	11	 | CH_3COOH (1:1)	84
2	OX:ChCl (2:1)	42	12	 | HCOOH (1:1)	92
3	Urea:ChCl (2:1)	54	13	 | CH_3COOH (1:1)	97
4	Urea:ZnCl₂ (1:2)	38	14	 | CH_3COOH (1:1) (0.1 mL)	88
5	PTSA:ChCl (2:1)	47	15	 | CH_3COOH (1:1) (0.2 mL)	97
6	glycerine:ChCl (1:5)	28	16	 | CH_3COOH (1:1) (0.3 mL)	97
7	 | HCOOH (1:1)	65	17	 | CH_3COOH (1:1) (0.4 mL)	97
8	 | CH_3COOH (1:1)	69	18	 | CH_3COOH (1:1) (0.5 mL)	97
9	 | HCOOH (1:1)	76	19	 | PhCOOH (1:1) (0.2 mL)	81
10	 | CH_3COOH (1:1)	79	20	 | HCl (1:1) (0.2 mL)	71

Table 3. Products of salicylaldehyde and ketoesters in coumarin Synthesis.

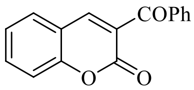




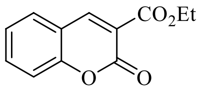
6a, 97%
116-118 °C 117-120 °C [33]
5 min.



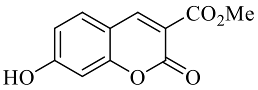
6**b**, 77%
180-182 °C 182-184 °C [30]
8 min.



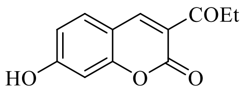
4c, 84%
135-137 °C 133-135 °C [29]
15 min.



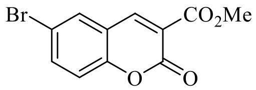
4d, 73%
88-89 °C 88-90 °C [30]
15 min.



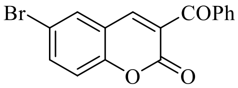
6e, 74%
264-266 °C 263-265 °C [34]
15 min.



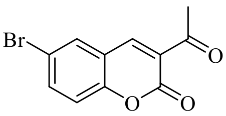
6f, 72%
173-175 °C 172-174 °C [36]
15 min.



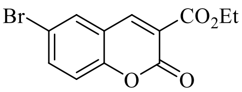
6g, 85%
182-184 °C 180-182 °C [34]
10 min.



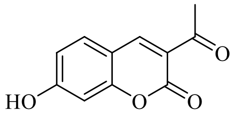
6**h**, 89%
176-178 °C 174-176 °C [34]
15 min.



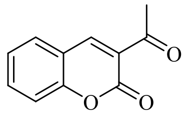
6i, 82%
234-236 °C 232-233 °C [40]
8 min.



6j, 91%
163-165 °C 164-166 °C [36]
5 min.



6k, 79%
232-234 °C 236-237 °C [36]
15 min.



6l, 97%
118-119 °C 121-122 °C [36]
10 min.

Table 4. Products of salicylaldehyde and ketoesters in coumarin Synthesis.

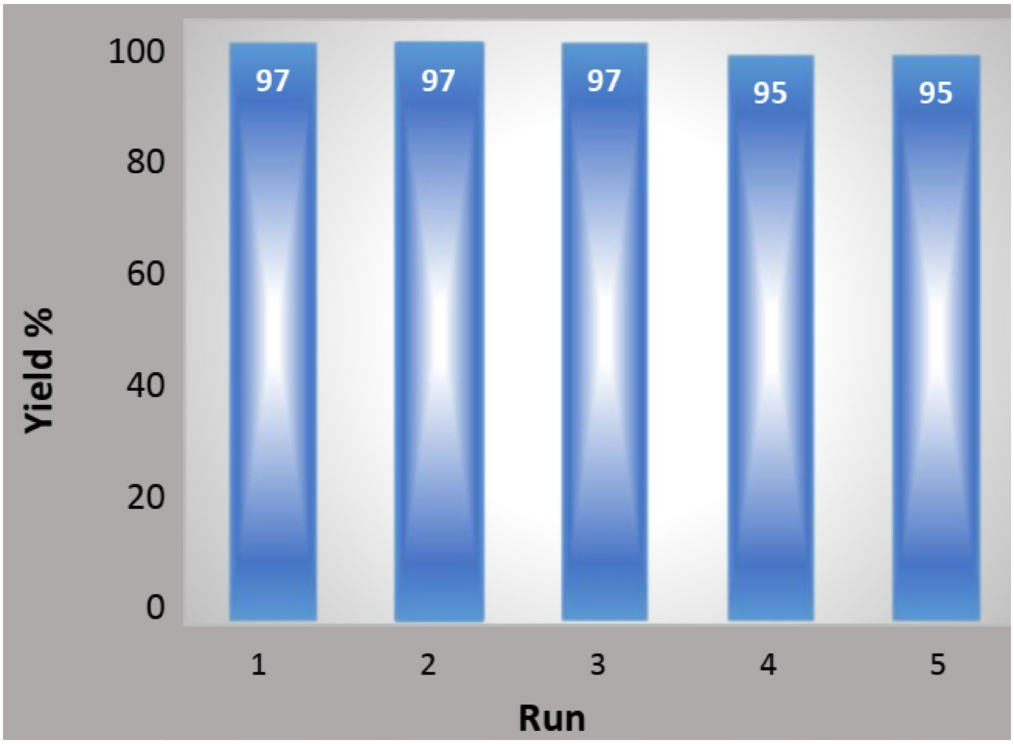


Fig. 6. Reusability study of the DES system for the synthesis of compound **6a**.

Data availability

All data generated during this study are included in this published article.

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Author contributions

Material preparation, data collection, and analysis were performed by Fatemeh Mohammad. Najmedin Azizi supervised and Writing- review & editing. The first draft of the manuscript was written by Zohreh Mirjafari. Javad Mokhtari: Formal analysis, Investigation, Software, Writing – review & editing. All authors reviewed the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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