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Fe(DS)₃, an efficient Lewis acid-surfactant-combined catalyst (LASC) for the one pot synthesis of chromeno[4,3-*b*]chromene derivatives by assembling the basic building blocks

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ABSTRACT

A highly efficient multicomponent heteroannulation protocol for the synthesis of a library of chromeno[4,3-*b*]chromene derivative has been developed by applying a Lewis acid-surfactant-combined catalyst (LASC) [Fe(DS)₃]. The LASC converted the initially floating reaction mass into a homogeneous mixture, which on stirring became a turbid emulsion of colloidal aggregates. The shape and size of the colloidal aggregates are confirmed by optical microscopy and DLS. The aqueous reaction medium, dual role of the catalyst in aqueous media, easy recovery of the catalyst, and high yield make the protocol attractive, sustainable, and economical.

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Environmental aspects triggered organic and medicinal chemists to focus on modification of known multicomponent coupling reactions (MCRs) with green characteristics. Use of water reduces the use of harmful organic solvents and is regarded as an important research topic in green chemistry.¹ In addition, water has unique physical and chemical properties, and by utilizing these it would be possible to realize reactivity or selectivity that cannot be attained in organic solvents.² However, organic reactions in water are often limited in scope due to poor solubility of the organic compounds. The solubility problem may be overcome by using surfactants, which solubilize organic materials or form colloidal dispersions with them in water. Lewis acid catalysis is one of the most powerful tools in modern organic synthesis,³ it has to be generally carried out under strictly anhydrous conditions because of the water-labile nature of most Lewis acids. To address this solubility issue, we designed to utilize surfactants with water-stable Lewis acid character for the Lewis acid catalyzed reactions in water.⁴ This type of catalyst, 'Lewis acid-surfactant-combined catalyst (LASC)', would act both as a catalyst to trigger the substrate molecules and as a surfactant to form colloidal particles. Therefore, it should, in principle, be possible to apply these catalysts to a wide variety of substrates. The surfactant-aided catalysis can tolerate drastic reaction conditions such as high temperature⁵ and should be applicable to various types of acid-catalyzed reactions. These advantages will enable us to study multi-component coupling reactions toward the synthesis of biologically active heterocyclic scaffolds in water.

Naturally occurring heterocyclic compounds containing coumarin core are one of the most active classes of compounds possessing a wide spectrum of biological activity.⁶ Many of the coumarin fused heterocycles show antitumor,⁷ antibacterial,⁸ antifungal,⁹ anticoagulant,¹⁰ anti-inflammatory,¹¹ and antiviral¹² activities. On the other hand, chromene moiety often appears as an important structural component in both biologically active and natural compounds. Chromene fragments occur in alkaloids, flavonoids, tocopherols, and anthocyanins. Moreover, functionally substituted chromenes have played increasing roles in synthetic approaches to promising compounds in the field of medicinal chemistry.^{13–16}

In continuation of our research program dedicated to the design and synthesis of novel heterocyclic systems using unconventional solvent based multicomponent reactions,¹⁷ we have started our investigation with the objective of developing a clean, efficient, and straightforward methodology utilizing a cheap, non-toxic, and environmentally benign catalyst. Very few methods have been reported for the synthesis of chromeno[4,3-*b*]chromene derivatives.¹⁸ However, these procedures have their own limitations, such as high reaction temperature, prolonged reaction time or low yields. In this Letter we wish to uncover a green three-component protocol for the synthesis of chromeno[4,3-*b*]chromene derivatives by assembling 4-hydroxycoumarin, aldehyde, and 1,3diketocompound (dimedone, cyclohexane-1,3-dione, and ethyl acetoacetate), advocating a 'Lewis acid-surfactant-combined catalyst', Fe(DS)₃¹⁹ in aqueous media.

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Scheme 1. Synthesis of chromeno[4,3-b]chromene derivative.

Table 1								
Screening	of	different	catalysts	for	the	synthesis ^a	of	chromeno[4,3-b]chromene
derivative								

Entry	Catalyst	Solvent	Time (h)	Yield ^b (%)
1	_	CH₃CN	20	Trace
2	p-Toluene sulfonic acid	CH_3CN	8	10
3	PEG–SO₃H	CH ₃ CN	8	10
4	ZnCl ₂	CH ₃ CN	6	20
5	MgCl ₂	CH ₃ CN	6	15
6	SiO ₂	CH ₃ CN	6	18
7	FeCl ₃	CH ₃ CN	6	40
8	FeCl ₃	DCM	6	25
9	FeCl ₃	DMF	6	35
10	FeCl ₃	H ₂ 0	6	42
11	FeCl ₃ /sodium dodecyl sulfate	H ₂ 0	4	56
12	FeCl ₃ /sodium dodecyl sulfate	CH_3CN	6	42
13	FeCl ₃ /sodium dodecyl sulfate	DCM	6	24
14	FeCl ₃ /sodium dodecyl sulfate	DMF	6	36
15	Sodium dodecyl sulfate (SDS)	H_2O	6	30
16	Dodecyl sulfonic acid (DSA)	H_2O	6	33

 a 4-Nitrobenzaldehyde (1 mmol), cyclohexane-1,3-dione (1 mmol), and 4-hydroxycoumarin (1 mmol) were stirred in 2.5 ml solvent in presence of 10 mol % catalyst at 70 °C.

^b Isolated yield of the pure product.

To develop a clean three component protocol for the formation of only chromeno[4,3-b]chromene, we have installed a large number of Brønsted and Lewis acid catalysts for the optimization of the reaction condition. In a pilot experiment, 4-nitrobenzaldehyde (1 mmol), cyclohexane-1,3-dione (1 mmol), and 4-hydroxycoumarin (1 mmol) were stirred in CH₃CN at 70 °C temperature (Scheme 1). It was evident that the three component coupling product, chromeno[4,3-b]chromene derivative was obtained in trace amount after 20 h (Table 1, entry 1). To accelerate the three-component reaction, we have applied a wide spectrum of Brønsted and Lewis acid catalysts like p-toluene sulfonic acid, PEG-SO₃H, ZnCl₂, MgCl₂, SiO₂, and FeCl₃ (Table 1). We found that for the three-component coupling protocol, Brønsted acids were not very much efficient as compared to the Lewis acid catalysts desiring the synthesis of the heterocyclic scaffold under the particular experimental condition. Again sodium dodecyl sulfate (SDS) and dodecyl sulfonic acid (DSA) were unable to show significant improvement of the desired product yield under the particular experimental condition (Table 1, entries 15 and 16). It was also evident that FeCl₃ responded well in comparison to other Lewis acid catalysts. Various solvents such as CH₃CN, DCM, DMF, and water were screened for the three-component coupling reaction. CH₃CN was taken as the primary choice of the solvent as in this solvent all the reactants remained as a homogeneous mixture. Table 1 also revealed that the efficiency of FeCl₃ was almost same in CH₃CN and water. One important facet of green chemistry is the eradication of solvents in chemical processes or the replacement of hazardous solvents with relatively benign solvents. Developing environmentally benign and economical syntheses is an area of research that is being vigorously pursued, and avoiding the use of harmful organic solvents is a fundamental strategy to achieving this. Hence, we have tried to synthesize the heterocyclic scaffold in aqueous media applying suitable catalyst combination and we have applied FeCl₃/sodium dodecyl sulfate catalyst combination to enhance the rate of the reaction. But very little improvement of the yield of the desired product was noticed by using the catalyst combination (Table 1, entry 11, bold).

In comparison with different acid catalysts, FeCl₃ proved to be the most efficient catalyst which gave higher yield (42%) within 6 h (Table 1, entry 10, bold). Probably due to the lower solubility of the reactants, the product was not produced efficiently under the above mentioned reaction conditions. Again in the presence of a surfactant, activity of the catalyst was not as pronounced as expected which may be due to water labile character of FeCl₃. The yield of the desired product was almost same when the experiments 7–9 were repeated in the presence of FeCl₃/sodium dodecyl sulfate combo-catalyst (Table 1, entries 12–14). The above results (Table 1, entries 10 and 11) encouraged us to think about a water-stable catalyst having both the surfactant property and strong Lewis acidity to promote the three-component reaction. We have examined a wide spectrum of 'Lewis acid-surfactantcombined catalyst (LASC)' such as Cu(dodecyl sulfate)₂ [Cu(DS)₂], Ni(dodecyl sulfate)₂ [Ni(DS)₂], Ti(dodecyl sulfate)₄ [Ti(DS)₄], $Zn(dodecyl sulfate)_2 [Zn(DS)_2]$, and $Fe(dodecyl sulfate)_3 [Fe(DS)_3]$ in search of a suitable condition to synthesize the heterocyclic scaffold in aqueous media. It is pertinent to mention that the addition of LASC converted the initially floating reaction mass into a homogeneous mixture, which on stirring became a turbid emulsion (Fig. 4). This observation implies that there was formation of micelles or colloidal aggregates. After extensive studies this reaction is optimized in aqueous media (Table 2, entry 5, bold) by using colloidal aggregates of Fe(DS)₃ (characterized by IR and elemental analysis). The average sizes of the colloidal particles formed from $[Fe(DS)_3]$ and the reaction mixture in water were measured by dynamic light scattering (DLS), and shape of the colloidal aggregates was nearly spherical with around 240 nm in diameter (Fig. 1b). Formation of emulsion droplets in the present reaction system was also confirmed by optical microscopy (Fig. 1a). Our studies reveal that the reaction rate depends on the size of colloidal aggregates. The colloidal aggregates formed by the Cu(DS)₂, Ni(DS)₂, Ti(DS)₄, Zn(DS)₂ are either very large or too small and thus these LASCs were not effective to catalyze the MCR.

To find the optimized amount of catalyst (as shown in Fig. 2), the reaction was carried out by varying the amount of the catalyst on the model reaction. The conversion of chromeno[4,3-*b*]chromene derivative increased linearly with the catalyst weight up to 10 mol % and became almost steady when the amount of catalyst was further increased beyond this. As the amount of the surfactant-type catalyst increases, the size of each droplet may decrease, because the emulsion system may become a microemulsion system. The smaller the droplets, the larger the sum of the surface area of the droplets and as a result, the organic phase and water can contact each other decreasing the solubility of the organic molecules in water. Therefore 10 mol % catalyst is sufficient to catalyze the reaction leading to expected coumarin fused heterocycle in excellent yield.

Initializing the optimal conditions of this new multicomponent domino process²⁰ we embarked on the library construction with 1,3-diketo compounds and 4-hydroxycoumarin with various aro-



Figure 1. (a) Optical microscopic image showing colloidal aggregates in the reaction media and (b) DLS study of the reaction media showing formation of aggregates.



Figure 2. Weight effect of the catalyst in the three-component coupling reaction.



Figure 3. ORTEP Diagram of compound 2b (CCDC No. 893672)

matic aldehydes bearing electron-donating as well as electronwithdrawing functionalities. The results are summarized in Table 3. All the aromatic aldehydes bearing electron-donating as well as electron-withdrawing functionalities reacted efficiently with 1,3diketo compounds to afford the desired chromeno[4,3-*b*]chromene derivatives in high yield (Table 3). It can be observed that the process withholds a wide variety of aldehydes and two symmetrical 1,3-diketo compounds providing a library of substituted chromeno[4,3-*b*]chromene derivatives with high purity. Besides, our methodology has been applied successfully on acyclic



Figure 4. Pictorial presentation of (a) colloidal aggregates formed by reaction mixture and $Fe(DS)_3$; (b) reaction mixture after completion of reaction and (c) reaction mixture after centrifugation of the reaction mixture.

Table 2
Screening of LASCs for the synthesis a of chromeno [4,3- b] chromene derivative

Entry	LASC	Time (h)	Yield ^b (%)
1	Cu[CH ₃ (CH ₂) ₁₁ OSO ₃] ₂	3	48
2	Ni[CH ₃ (CH ₂) ₁₁ OSO ₃] ₂	3	45
3	Ti[CH ₃ (CH ₂) ₁₁ OSO ₃] ₄	3	44
4	$Zn[CH_3(CH_2)_{11}OSO_3]_2$	3	40
5	Fe[CH ₃ (CH ₂) ₁₁ OSO ₃] ₃	1.5	93

 a 4-Nitrobenzaldehyde (1 mmol), cyclohexane-1,3-dione (1 mmol), and 4-hydroxycoumarin (1 mmol) were stirred in 2.5 ml water in presence of 10 mol % LASC at 70 $^{\circ}$ C.

^b Isolated yield of the pure product.

unsymmetrical 1,3-dicarbonyl compound (Table 3, entries 26–28) and aliphatic aldehyde (Table 3, entries 13 and 25) and corresponding chromeno[4,3-*b*]chromene derivatives were obtained in excellent yields without any byproduct. The progress of the reaction was monitored by TLC. In all the cases, the reaction was completed within 1.5–2.5 h and the products could be isolated by simple filtration of the precipitate formed. The structures of desired products were characterized by IR, ¹H, ¹³C NMR spectral data, as well as elemental analysis. The X-ray crystal structure of **2b**²¹, (Fig. 3) further confirmed the product identity.

A reasonable mechanism is presented in Scheme 2. The organic fragment ($[CH_3(CH_2)_{11}OSO_3]_3$) of the catalyst Fe(DS)₃ forms micelles in presence of water with the hydrophilic part outside and the hydrophobic part inside. The result of Table 1, entries 15 and 16 clearly indicates that in absence of Fe³⁺, only SDS and DSA cannot catalyze the MCR. Table 1, entries 15, 16 and Table 2, entry 5 reveal that Fe³⁺ acts as an efficient Lewis acid catalyst for the three

Table 3

Substrate scope for the synthesis of chromeno[4,3-b]chromene derivatives^a



Entry	R	1,3-Dicarbonyl	Product	Time (h)	Yield ^b (%)
1	C ₆ H ₅	0	1a	2.0	87
2	$3 - NO_2 - C_6 H_4$		1b	1.5	90
3	$4 - NO_2 - C_6 H_4$		1c	1.5	93
4	$2-Cl-C_6H_4$		1d	1.5	88
5	$4-Cl-C_6H_4$	\sim .0	1e	1.5	90
6	$4-F-C_6H_4$		1f	1.5	92
7	$4-OCH_3-C_6H_4$		1g	2.5	82
8	$3-CH_3-C_6H_4$		1h	2.0	85
9	$4-CH_{3}-C_{6}H_{4}$		1i	2.0	87
10	3-OH-4-OCH ₃ -C ₆ H ₃		1j	2.5	83
11	3-0CH ₃ -4-0H-C ₆ H ₃		1k	2.5	82
12	$4-OH-C_6H_4$		11	2.5	83
13	CH ₂ CH ₃		1m	3.0	80
14	C ₆ H ₅	0	2a	2.0	86
15	$3 - NO_2 - C_6 H_4$		2b	1.5	90
16	$4 - NO_2 - C_6 H_4$		2c	1.5	92
17	$2-Cl-C_6H_4$	\rightarrow	2d	1.5	86
18	$4-Cl-C_6H_4$	$\rangle \sim 0$	2e	1.5	89
19	$4-F-C_6H_4$		2f	1.5	92
20	$4-OCH_3-C_6H_4$		2g	2.5	80
21	3-CH ₃ -C ₆ H ₄		2h	2.0	82
22	$4-CH_{3}-C_{6}H_{4}$		2i	2.0	84
23	3-OH-4-OCH ₃ -C ₆ H ₃		2j	2.5	81
24	3-0CH ₃ -4-0H-C ₆ H ₃		2k	2.5	81
25	CH ₂ CH ₃		21	3.0	78
26	CeH5	0 0	3a	2.0	73
27	$3-NO_2-C_6H_4$	Û Î .	3b	1.5	78
28	$4-OCH_3-C_6H_4$	< <u>0</u>	3c	2.5	70

^a Aldehyde (1 mmol), 1,3-dicarbonyl (1 mmol), and 4-hydroxycoumarin (1 mmol) were stirred in 2.5 ml H₂O in presence of 10 mol % Fe(DS)₃ at 70 °C. ^b Isolated yield of the pure product.



Scheme 2. Plausible mechanism for the formation of chromeno[4,3-b]chromene derivatives.

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component coupling reaction and it also indicates presence of Fe³⁺ inside the hydrophobic core of the micelle, as in the micellar solution of the organic reactants (1,3-diketocompound, 4-hydroxycoumarin, and aldehydes) are forced inside the hydrophobic core of the micelle. Fe(DS)₃ shows dual role in organic reactions as a catalyst to activate the substrate molecules and as a phase transfer catalyst to solubilize organic reactants in aqueous medium. The reaction driving force in micelles may be related to the hydrophobic force which compresses the reactants together in a highly compact arrangement of complexes together within a restricted hydrophobic domain. By coordinating with Fe³⁺ ion, 1,3-diketocompound and 4-hydroxycoumarin generate a hydrophobic environment around Fe³⁺ ion when all the reactants and the catalyst Fe(DS)₃ were stirred in water. Consequently, during the formation of the micelle Fe³⁺ enters within the hydrophobic domain. ²² The mechanism of the reaction involves. Knoevenagel condensation. Michael addition, and then intra molecular cyclization catalyzed by Fe³⁺ as presented in Scheme 2. The LASC is accompanied by inherent Lewis acidity of Fe³⁺, which is capable of bonding with carbonyl oxygen of the aldehyde assisting the nucleophilic attack by the 1,3-diketo compound and in turn facilitates the formation of intermediate A. Knoevenagel condensation product (A) as an intermediate in the above reaction was confirmed by isolating the same intermediate A from the reaction mixture at halfway of the reaction and performing a two component reaction.²³ Then the intermediate **A** undergoes Fe³⁺ catalyzed Michael addition reaction by the α -position of the hydroxyl functionality of 4hydroxycoumarin with the formation of the intermediate **B**. Finally, Fe³⁺ promoted nucleophilic attack by the oxygen atom of the hydroxyl group and elimination of water leads to the formation of the desired coumarin fused heterocyclic derivatives.

A catalyst is more interesting when it can be easily recovered and re-used. From green chemistry point of view, it is desirable, to develop a work up procedure without using any organic solvent. In addition, the development of a protocol for recovery and reuse of the catalysts is indispensable to apply the LASC system to largescale syntheses. Therefore, it is worthy to mention that the separation of the catalyst-water mixture from the water insoluble product can be done by centrifugation of the reaction mixture of a LASC catalyzed three component coupling reaction as presented in Figure 4c. It is noted that this procedure enables, in principle, the recovery and reuse of LASCs and the separation of the organic products without using organic solvents. In this procedure, after completion of the reaction, the crude product (insoluble in water) was filtered and washed with ethanol for further purification. In order to recover the catalyst, H₂O was evaporated under reduced pressure, and the resulting solid was washed with diethyl ether, and dried under reduced pressure. The reusability of catalyst was tested for the reaction of 4-nitrobenzaldehdye, cyclohexane-1,3dione, and 4-hydroxycoumarin. The catalyst was recovered in good proportion (85-90%) after each of the new set of reactions and we were able to recycle the catalyst for four times with almost same catalytic activity.

In summary, we have developed a very practical carbon-carbon bond forming reaction in water. The key is the use of newly synthesized Lewis acid-surfactant-combined catalyst. While most organic substrates are not soluble in water, stable colloidal dispersions are formed immediately by combining the catalyst and organic materials in water, and Lewis acid-catalyzed organic reactions proceed smoothly. This simple, environmentally benign and convenient methodology extends the scope toward a wide spectrum of novel compounds possessing an important structural subunit of a variety of biologically active molecules. The surfactant-type catalyst described in this article will contribute to progress in chemical processes by reducing the use of organic solvents.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tet-let.2013.04.001. These data include MOL files and InChiKeys of the most important compounds described in this article.

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- Preparation of LASC, Fe(DS)₃: To a solution of SDS (3.4 g, 11.6 mmol) in water (100 ml) was added a solution of FeCl₃ (0.63 g, 3.85 mmol) in water (20 ml) at room temperature. Yellow precipitates appeared immediately, and the mixture was stirred for 30 min. The Yellow solid was filtered, washed with water (50 ml × 5), and dried under reduced pressure. Mp 210 °C; IR (KBr) 1170, 1315 cm⁻¹; Calcd for C₃₆H₇₅O₁₂S₃Fe·3H₂O: C, 47.72;
- H, 9.01; S, 10.62%. Found: C, 47.69; H, 8.99; S, 10.60%.
 20. General procedure for the synthesis of chromeno[4,3-b]chromene derivatives: A mixture of 4-hydroxycoumarin (1.0 mmol), aromatic aldehyde (1 mmol), 1,3-diketo compound (cyclohexane-1,3-dione, dimedone, and ethyl acetoacetate) (1.0 mmol) and Fe(DS)₃ (10 mol%) was taken in 2.5 ml water. The mixture was stirred at 70 °C for a required period of time (TLC). After completion of each reaction, the crude product (insoluble in water-catalyst mixture) was filtered and it was washed with water (15 ml × 5) and ethanol (5 ml × 3). The isolated

product was recrystallized from ethanol to get the pure product.

- 7-(4-Nitro-phenyl)-7,9,10,11-tetrahydro-chromeno[4,3-b]chromene-6,8dione(**1c**): Characteristic: White solid; mp: 224 °C; IR (KBr): 2944, 1720, 1660, 1527 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.93–2.1 (2H, m), 2.28–2.42 (2H, m), 2.67–2.89 (2H, m), 4.98 (1H, s), 7.24–7.33 (2H, m), 7.46–7.55 (3H, m), 7.81–7.84 (1H, m), 8.02 (2H, t, *J* = 9.1 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 20.1, 27.1, 33.5, 36.6, 105.3, 113.1, 115.2, 116.8, 117.0, 123.3, 123.7, 124.7, 129.6, 130.0, 132.7, 146.8, 149.8, 152.6, 154.3, 160.4, 164.2, 196.0; Anal. Calcd for C₂₂H₁₅NO₆: C 67.86, H 3.88, N 3.60%. Found: C 67.83, H 3.84, N 3.64%.
- Crystallographic data for the structure 2b has been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 893672. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 01223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
- Ribeiro, R. T.; Dias, J. M. M.; Pereira, G. A. L.; Freitas, D. V.; Monteiro, M.; Filho, P. E. C.; Raele, R. A.; Fontes, A.; Navarro, M.; Santos, B. S. *Green Chem.* **2013**, *15*, 1061.
- 23. Knoevenagel condensation product of dimedone was prepared by heating the mixture of benzaldehyde (1.0 mmol), dimedone (1.0 mmol), and Fe(DS)₃ (10 mol %) in 2.5 ml water at 70 °C for 30 min. When a two-component coupling reaction between the Knoevenagel condensation product (**A**) and 4-hydroxycoumarin was performed in presence of Fe(DS)₃ (10 mol %) in 5 ml water at 70 °C, 90% of **2a** was isolated after 1.5 h.

