One-pot synthesis of biologically important xanthene derivatives using $[(Et_3N)_2SO][HSO_4]_2$ as a novel and green IL-based catalyst under solvent-free conditions

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Abstract

In this article, we introduce an efficient and reusable catalyst for the synthesis of biologically active xanthene derivatives through a one-pot condensation of aldehydes, 2-naphthol, and dimedone, using the novel dicationic Brönsted acidic ionic liquid $[(Et_3N)_2SO][HSO_4]_2$. The catalyst was characterized using ^1H NMR, ^{13}C NMR, and MS (ESI). The noteworthy advantages of the present method were short reaction times, high product yields, straightforward procedure, and easy work-up procedure. In addition, the catalyst can be easily separated from the reaction mixture by filtration and reused in five consecutive cycles without significant loss in catalytic activity.

Introduction

Creation of structurally complex organic compounds from simple substrates is the first and most important purpose of organic synthesis in recent years [1]. As a powerful and ideal protocol for the construction of different heterocycles and natural products, Multicomponent reactions (MCRs) are very significant tool for atom economic synthesis of highly valuable products with good to excellent yields and the benefit of time saving and using important source of molecular diversity starting from cheap and readily available materials under catalytic solvent-free conditions [2-4]. Performing chemical reactions under solvent-free conditions is an important technique in green chemistry in which many compounds could be synthesized in an effective and environment friendly manner. Solvent-free synthesis has several benefits compared with the classical synthetic methods; these advantages include: (i) safer reaction profile, (ii) higher yield of product, (iii) shorter reaction time, (iv) higher selectivity in many reactions, (v) easier work-up, (vi) maximum incorporation of the reactants into the aim product, (vii) fewer energy requirement to promote reaction, (viii) prevention of using harmful solvents, and (ix) prevention or minimization of waste/by-products [5,6].

Through both laboratory and industrial scales, Brönsted acids are widely used in the synthesis of organic products [6,7]. Despite encountered serious concerns, homogeneous Brönsted acids possess some drawbacks, mainly due to the production of hazardous gas, and being corrosive. In this regard, safe or less hazardous compounds are required for replacement of the mentioned homogeneous acid catalysts. A new emerging type of greener solvents and catalysts that have received widespread attention as an eco-friendly reaction medium is ionic liquids (ILs) [8].

The unusual properties of ILs such as negligible vapour pressure, wide liquid range, excellent solubility, and good selectivity have made a variety of applications such as solvent, catalysts, gas adsorbents, and chromatography stationary phases in recent years [9-12]. Acidic Brönsted-type ionic liquids with acidic properties are one of the most important ionic liquid derivatives that are replaced with the most common acids used in labs and in industry [13,14]. Furthermore, acidic ILs possesses the advantages of both liquid acid and solid acid catalysts such as water solubility, recyclable, high acid density, easy separation, and reusability [15]. In this context, acidic ILs is now widely acknowledged as a new class of advanced acidic catalyst for many organic transformations [16-19].

Benzoxanthenes and their derivatives have a great deal of importance due to their numerous biological activities, including their antibacterial and anti-inflammatory in medicinal chemistry and biology [20]. They are used as fluorescent compounds in laser technology and widely used as building blocks in dye chemistry [21]. The simplest and practical preparation of benzoxanthenes and its derivatives, involve the condensation reaction of carbonyl compounds with 2-naphthol derivatives in the presence of acidic catalysts [22]. In light of their wide range of industrial applications, numerous protocols have been reported in the preparation of biologically important 14-aryl-14H-dibenzo [a,j] xanthenes [23-27] and 1,8-dioxo octahydroxanthenes [28-30] using a variety of catalysts or promoter in the literature. However, the majority of acid catalysts are highly corrosive and are not easy to recover for reuse. Because of these drawbacks, the reaction has been improved by mixing aldehydes with 2-naphthol or dimedone in the presence of acidic catalysts, such as magnetic nano-Fe_3O_4-supported Lewis acidic ionic liquid, a "quasi-homogeneous" catalyst composed of 3-sulfobutyl-1-(3-propyltriethoxysilane) imidazolium hydrogen sulfate onto the surface of silica-coated Fe_3O_4 nanoparticles (AIL@MNP) [31], 1, 3-disulfonic acid imidazolium hydrogen sulfate (DSIMHS)[32], sulfonic acid functionalized imidazolium salts (SAFIS)[33], the task-specific ionic liquid ([MIMPS]HSO_4) [34], and [Et_3NH][H_2PO_4] [35]. Among the most effective acidic catalysts, magnetic acidic ionic liquid are frequently utilized for the preparation of xanthene derivatives due to the high productivity and easy separation using an external magnet.

In continuation of our studies on the development of practical, safe, and environmentally friendly procedures for some important transformations [36-39], we had an opportunity to explore the catalytic activity of a novel IL-based catalyst,

$[(Et_3N)_2SO][HSO_4]_2$, with Brönsted acid sites towards the synthesis of benzoxanthenes derivatives under solvent-free reaction conditions (Scheme 1).
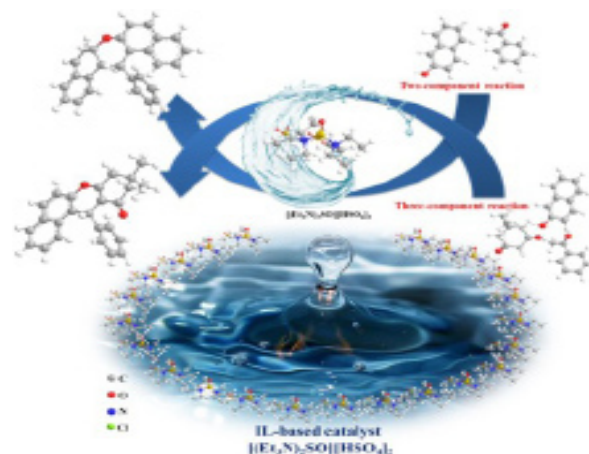
Scheme 1: Schematic illustration of synthesis of xanthene derivatives using $[(Et_3N)_2SO][HSO_4]_2$*

Experimental

Material and apparatus

All chemicals were purchased from Merck (Germany) and Fluka (Switzerland), and used with no further purification. Melting points were measured on an Electrothermal 9100 apparatus. Progress of reactions was monitored by thin-layer chromatography (TLC). ^1H and ^{13}C NMR spectra were measured with a Bruker DRX-500 AVANCE spectrometer at 500 and 75 MHz, respectively. Mass spectra were recorded on Aligent Technologies 5957C VL MSD with Triple-Axis Detector operating at ionization potential of 70 eV.

Preparation of ionic liquid $[(Et_3N)_2SO]Cl_2$

Triethylamine (10 mmol, 1.39 mL) and dry dichloromethane (50 mL) was added to a three-neck round-bottom flask (100 mL) equipped with a condenser, and the system was inserted into the ice bath. Thionyl chloride (5 mmol, 0.36 mL) was then added dropwise throughout 30 min. The mixture was stirred for another 12h at room temperature. The ionic liquid [$(Et_3N)_2SO$]Cl_2 was obtained by removing dichloromethane. Subsequently, the IL was washed with dry diethyl ether (3×10 mL) and heated in an oven at 70°C to acquire the pure IL.

Preparation of ionic liquid $[(Et_3N)_2SO][HSO_4]_2$

A round bottom flask (50 mL) was charged with the as-synthesized [$(Et_3N)_2SO$]Cl_2 (10 g, 36 mmol) dispersed in dry dichloromethane (30 mL), and then sulfuric acid (7.056 g, 72 mmol) was added throughout 30 min at 0-5°C. The resulting mixture was stirred under N_2 atmosphere for 2h. The reaction progress was followed by pH monitoring. The solvent was removed by rotary evaporation to obtain the product, which washed with dry diethyl ether (3×10 mL) and dried in an oven at 70°C throughout 5h to give [$(Et_3N)_2SO$][HSO_4]$_2$ as viscous brown oil with 91% yield (Scheme 2).
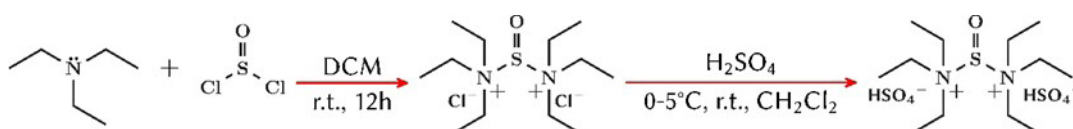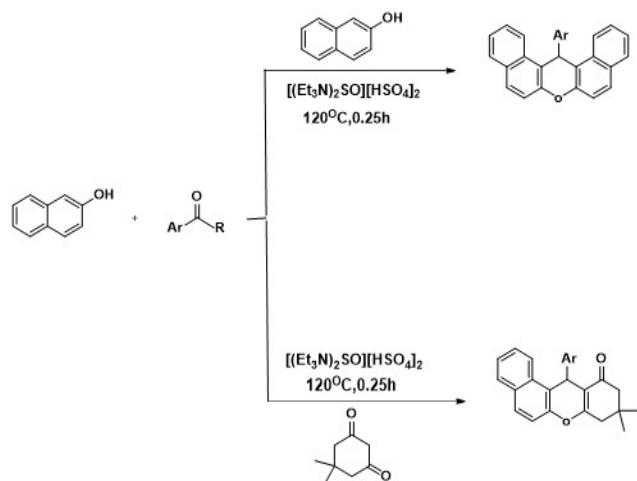

Scheme 2: Synthesis of $[(Et_3N)_2SO][HSO_4]_2$*

General procedure for the preparation of 14-aryl-14H-dibenzo[*a,j*]xanthenes

A mixture of aldehyde (1 mmol), 2-naphthol (2 mmol) and [(Et$_3$N)$_2$SO][HSO$_4$]$_2$ (0.15 mmol) was stirred at 120°C for the appropriate time indicated in Table 2. The progress of the reactions was monitored by TLC (Ethyl acetate/*n*-hexane, 1:5). After completion of the reaction, the reaction mixture was cooled to room temperature, the crude product was heated in ethanol (5 mL), and the catalyst was removed by filtration. The pure product was obtained by cooling of the filtrate (Scheme 3).

General procedure for the preparation of tetrahydrobenzo xanthene-11-ones derivatives

A mixture of aldehyde (1 mmol), 2-naphthols (1 mmol), dimedone (1.1 mmol) and [(Et$_3$N)$_2$SO][HSO$_4$]$_2$ (0.15 mmol) was stirred at 120°C for the appropriate time indicated in Table 2. The progress of reactions was monitored by TLC (Ethyl acetate/*n*-hexane, 1:5). After completion of the reaction, the reaction mixture was cooled to room temperature, the crude product was heated in ethanol (5 mL), and the catalyst was removed by filtration. The pure product was obtained by cooling of the filtrate (Scheme 3).

Scheme 3: Synthesis of xanthene derivatives in the presence of [(Et$_3$N)$_2$SO][HSO$_4$]$_2$[*]

Spectral data of compound (Table 2, Entry 4b)

R (KBr): mmax = 3,227, 3,081, 2,961, 2,891, 1,630, 1,518, 1,451, 1,381, 1,238, 1,182, 1,030, 841, 698, 617, 530, 442 cm-1; ^{1}H NMR (300 MHz, DMSO-d$_6$): d = 9.86 (s, 1H), 8.08 (d, *J* = 7.2 Hz, 2H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.9 Hz, 1H), 7.45 (d, *J* = 7.3 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.15 (s, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 5.5 (s, 1H), 2.58 and 2.69 (AB system, *J* = 17.6 Hz, 2H), 2.13 and 2.34 (AB system, *J* = 16.3 Hz, 2H), 1.06 (s, 3H), 0.86 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d$_6$): d = 196.4, 164.9, 157.1, 152.5, 148.1, 146.3, 132.8, 130.8, 129.9, 129.8, 125.9, 123.8, 117.8, 114.5, 114.0, 112.6, 105.5, 50.4, 34.9, 32.2, 29.2, 26.6 ppm.

Spectral data of compound (Table 2, Entry 8b)

R (KBr): mmax = 3054, 2954 , 1650, 1511, 1373,1230, 1022, 809; 1H NMR (300 MHz, DMSO-d$_6$): d (ppm) 8.03(d, *J*=2Hz, 1H), 7.80(t, *J*=3 Hz, 2H), 7.34-7.46(m, *J*= 1Hz, 5H), 7.28(s, 1H), 7.21(t, *J*=2Hz, 2H), 7.06-7.07(t, *J*=1 Hz, 1H), 5.74(s, 1H, CH), 2.58(s, 2H, CH$_2$), 2.25-2.23(q, *J*=3 Hz, 4H, CH$_2$),1.13(s, 3H, CH$_3$), 0.98(s, 3H, CH$_3$); ^{13}C NMR (75 MHz, DMSO-d$_6$): d (ppm) 196.8, 163.8, 147.7, 144.7, 131.48, 131.40, 128.8, 128.4, 128.3, 128.2, 126.9, 126.2, 124.8, 123.6, 117.7, 117.0, 114.2, 50.91, 41.41, 34.71, 32.26, 29.30, 27.16.

Spectral data of compound (Table 2, Entry 8a)

R (KBr): mmax = 3421, 2908, 1589, 1241, 809; ^{1}H NMR (300 MHz, DMSO-d$_6$): d (ppm) 8.42(d, *J*=2Hz, 2H), 7.80-7.85(m, *J*=3Hz, 4H), 7.49-7.61(m, *J*=5Hz, 6H), 7.44(t, *J*=2Hz, 2H) 7.18(t, *J*=2Hz, 2H), 7.02(t, *J*= 2Hz, 1H), 6.51 (s, 1H, CH); ^{13}C NMR (75 MHz, DMSO-d$_6$): d (ppm) 148.8, 145.1, 131.5, 131.1, 128.9, 128.8, 128.5, 128.3, 126.8, 126.4, 124.3, 122.7, 118.1, 117.4, 38.13.

Spectral data of compound (Table 2, Entry 1a)

R (KBr): mmax = 3428, 2915, 1589, 1241, 809; ^{1}H NMR (300 MHz, DMSO-d$_6$) d(ppm) 8.32(d, *J*= 1Hz, 2H), 7.79-7.84(dd, *J*= 2Hz, 4H), 7.60(t, *J*= 2Hz, 2H), 7.41-7.49(m, *J*= 1Hz, 6H),7.11(d, *J*=2Hz, 2H), 6.46 (s, 1H, CH); ^{13}C NMR (75 MHz, DMSO-d$_6$): d (ppm) 36.3, 148.5, 144.8, 131.2, 130.8, 128.7, 128.3, 128.1, 126.6, 126.2, 124.0, 122.5, 117.8, 117.1, 37.89.

Results and Discussion

Characterization of [(Et$_3$N)$_2$SO][HSO$_4$]$_2$

The novel dicationic ionic liquid catalyst was prepared by condensation of 2 eq Et$_3$N with thionyl chloride and then acidification of the resulting salt with one equivalent amount of concentrated sulfuric acid. The structure of prepared IL catalyst, [(Et$_3$N)SO[HSO$_4$]$_2$ was identified by instrumental analysis ^{1}H NMR (Figure 1), ^{13}C NMR (Figure 2) and MS spectra (Figure 3).
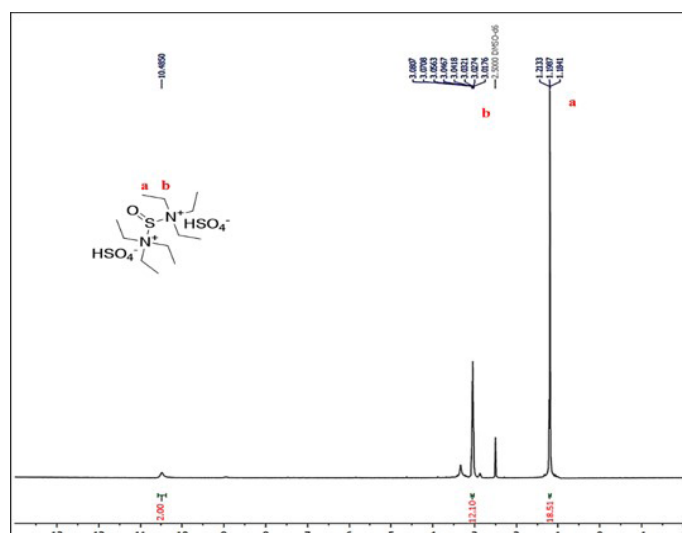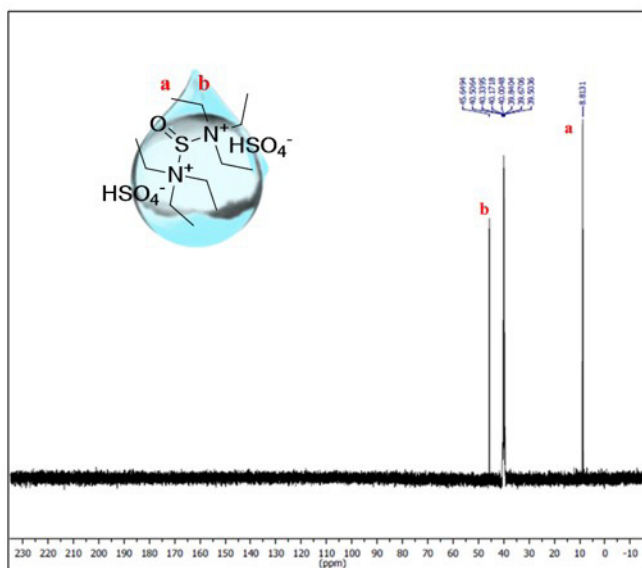

Figure 1: ^{1}H NMR spectrum of [(Et$_3$N)$_2$SO][HSO$_4$]$_2$

Figure 2: ^{13}C NMR spectrum of $[(Et_3N)_2SO][HSO_4]_2$

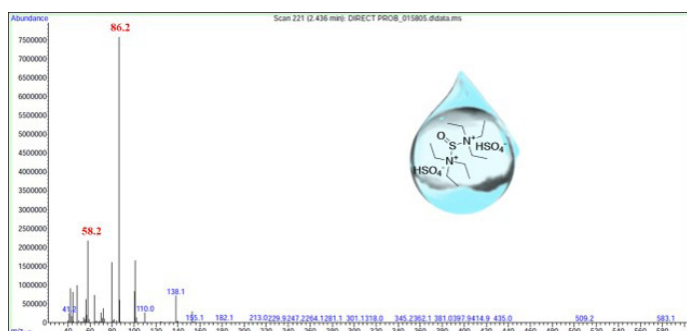**Figure 3:** Mass spectrum of $[(Et_3N)_2SO][HSO_4]_2$

The ^{1}H NMR and ^{13}C NMR spectra of the prepared IL in DMSO-d_6 are shown in Figures 1 and 2. Regarding the data observed from ^{1}H NMR spectrum of the catalyst, the peak related to the acidic hydrogens of HSO_4^- located in 10.63 ppm. The catalyst **4** showed two sharp peaks in the ^{1}H NMR spectrum at δ 1.18-1.21 (t, 18, *J* = 10 Hz) and 3.01-3.04 (q, 6H, *J* = 10 Hz) for ethyl protons of the IL due to the two diastereotopic methylene hydrogens in the catalyst.

The ^{13}C NMR spectrum of **4** showed two peaks assigned to C_a and C_b in the triethyl moieties. The ^{13}C NMR spectral data of $[(Et_3N)_2SO][HSO_4]_2$ ionic liquid (DMSO-d_6, 125 MHz) also showed two peaks at δ 8.81 and 45.64 (Figure 2). MS (ESI) spectra of $[(Et_3N)_2SO][HSO_4]_2$ ionic liquid showed two peaks at 86.2 *m/z* and 58.2 *m/z* (Figure 3).

Evaluation of catalytic activity of $[(Et_3N)_2SO][HSO_4]_2$

The condensation of various aldehydes, and 2-naphthol/dimedone in the presence of $[(Et3N)_2SO][HSO_4]_2$ for the preparation of xanthenes derivatives has been studied. The effects of different parameters on the model reaction were discussed in Table 1.

Initially, in order to optimize the reaction parameters, we investigated the catalytic activity of $[(Et3N)_2SO][HSO_4]_2$ in the synthesis of xanthene derivatives under different reaction conditions, using the condensation reaction of benzaldehyde and 2-naphthol as a model reaction. As shown in Table 1, among the tested solvents, such as CH_3OH, CH_3CH_2OH, CH_3CN, $CHCl_3$, THF, H_2O and a solvent-free system the best result was obtained after 10 min under solvent-free conditions in excellent yield (91%). When the same reaction was performed in the absence of the catalyst, the corresponding product was obtained in only <5% yield, whereas, $[(Et_3N)_2SO][HSO_4]_2$ in excess of 0.2 eq did not improve the yield to a greater extent (Table 1, entries ?).

Table 1: Optimization of model reaction catalyzed by $[(Et_3N)_2SO][HSO_4]_2$ for synthesis of xanthenes derivatives [a, b].

Entry	Solvent	Catalyst Loading (mol%)	Temperature (°C)	Time (min)	Yield (%)
1	CH_3OH	15	reflux	240	44[a], 45[b]
2	CH_3CH_2OH	15	reflux	240	49[a], 51[b]
3	CH_3CN	15	reflux	240	32[a], 39[b]
4	$CHCl_3$	15	reflux	240	59[a], 63[b]
5	THF	15	reflux	240	73[a], 78[b]
6	H_2O	15	reflux	240	Trace
7	Solvent-free	15	90	240	Trace
8	Solvent-free	15	100	60	80[a], 82[b]
9	Solvent-free	15	120	15	93[a], 95[b]
10	Solvent-free	10	120	60	85[a], 88[b]
11	Solvent-free	20	120	15	93[a], 93[b]
12	Solvent-free	-	120	240	Trace

[a] Reaction conditions: aldehyde (1 mmol), 2-naphthol (2 mmol), and $[(Et_3N)_2SO][HSO_4]_2$ (0.15 mmol)
[b] Reaction conditions: aldehyde (1 mmol), 2-naphthols (1 mmol), dimedone (1.1 mmol), and $[(Et_3N)_2SO][HSO_4]_2$ (0.15 mmol).
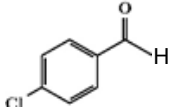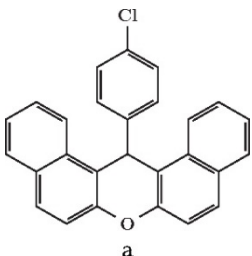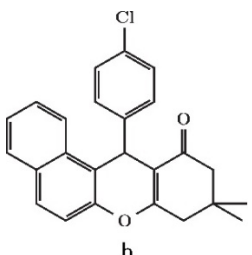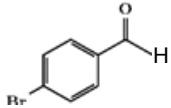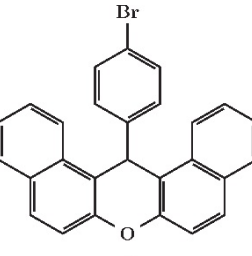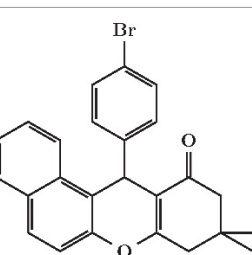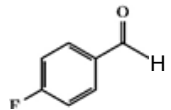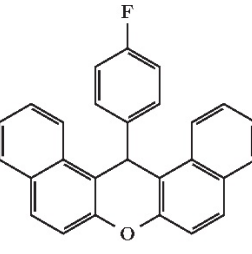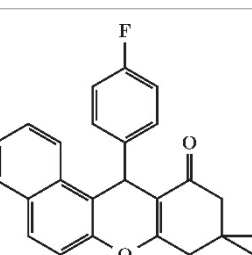
After optimizing the conditions, we next examined the scope and generality of this method with respect to various aromatic aldehydes with electron-withdrawing and electron-donating to prepare 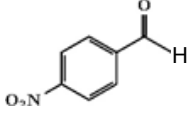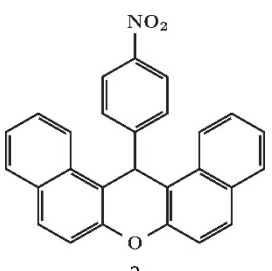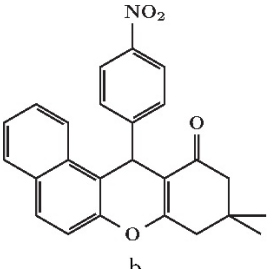a series o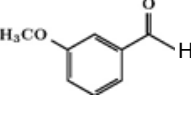f xanthene derivatives with good to high yields (Table 2). The present methodology afforded good to high yields of the products within short times (10-30 min).
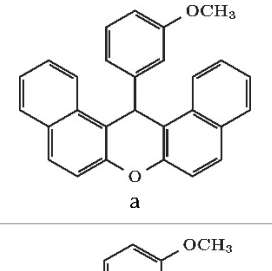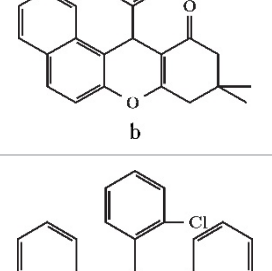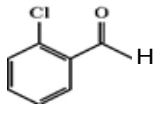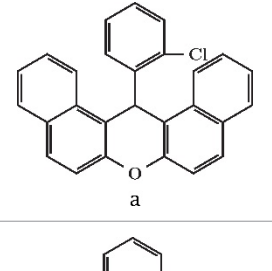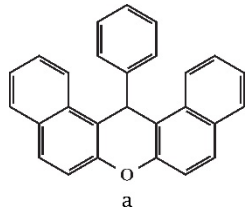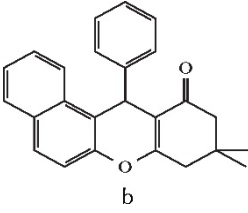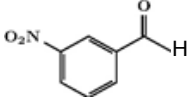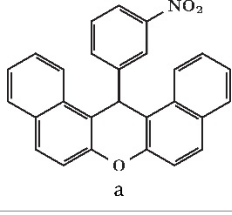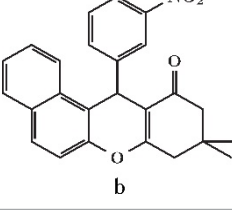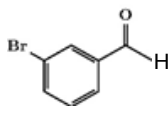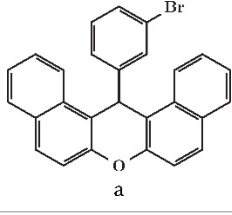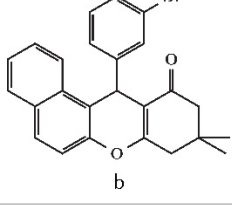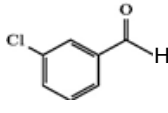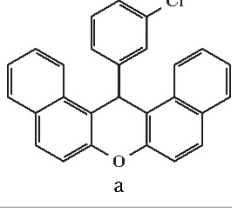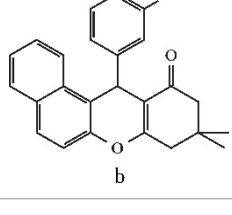
To further show the applicability of this method, the preparation of tetrahydrobenzo[*a*]xanthene-11-one derivative was also

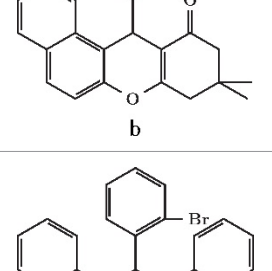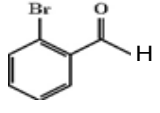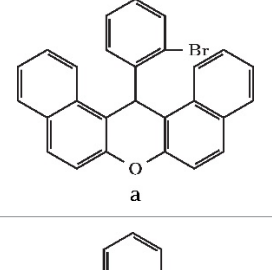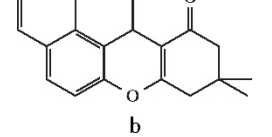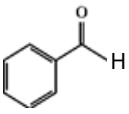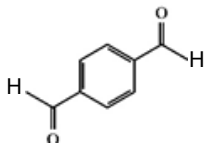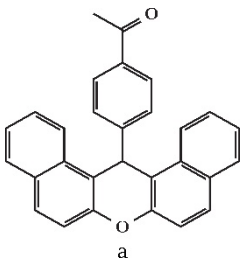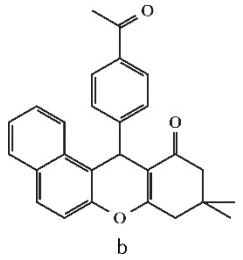investigated. A variety of aromatic aldehydes bearing electron-withdrawing groups (such as nitro and halide), electron-donating groups (such as methoxy), and dimedone were treated with 2-naphthol under the same experimental conditions, and the corresponding products were obtained in good to high yields without any difficulties (Table 2).

Table 2: Catalytic performance of $[(Et_3N)_2SO] [HSO_4]_2$ for synthesis of xanthenes derivatives [a, b].

Entry	Substrate	Product	Time (min)	Yield[c] (%)	Melting Point (°C)
1		a	15	93	284-286 [40]
		b	16	91	181-183 [33]
2		a	13	90	297-298 [40]
		b	16	93	184-186 [33]
3		a	10	80	239-241 [40]
		b	11	84	250-252 [41]

Entry	Substrate	Product	Time (min)	Yield[c] (%)	Melting Point (°C)
4		a	10	89	312-314 [42]
		b	13	85	174-178 [43]
5		a	30	66	210-211 [?]
		b	33	64	204-205 [43]
6		a	20	98	221-222 [43]
		b	25	97	191-192 [?]
7		a	14	99	169-171 [33]
		b	15	98	250-251 [43]

Entry	Substrate	Product	Time (min)	Yield[c] (%)	Melting Point (°C)
8		a	20	75	186-188 [42]
		b	22	77	148-150 [43]
9		a	16	89	214 [42]
		b	15	87	169-171 [33]
10		a	16	91	186-188 [32]
		b	18	87	159-162 [33]
11		a	17	83	207-209 [?]
		b	16	81	175-178 [33]

Entry	Substrate	Product	Time (min)	Yield[c] (%)	Melting Point (ºC)
12		a	15	77	202-203 [42]
		b	15	80	203-205 [32]

[a] Reaction conditions: aldehyde (1 mmol), 2-naphthol (2 mmol) and $[(Et_3N)_2SO][HSO_4]_2$ (0.15 mmol), at 120 °C under solvent-free conditions.

[b] Reaction conditions: aldehyde (1 mmol), 2-naphthols (1 mmol), dimedone (1.1 mmol) and $[(Et_3N)_2SO][HSO_4]_2$ (0.15 mmol), at 120 °C under solvent-free conditions.

[c] Isolated yield.

In order to assess the efficiency and generality of this methodology, the obtained result from the reactions have been compared with those of the previously reported methods using acidic ionic liquid catalysts (Tables 3). It was found that the $[(Et_3N)_2SO][HSO_4]_2$ is a fairly good reagent for this reaction with respect to reaction time, yield of product, and amount of the catalyst.

Table 3: Comparison of catalytic activities of different catalysts reaction for synthesis of xanthenes derivatives.

Entry	Catalytic System	Temperature (ºC)	Time (min)	Yield (%)
1	AIL@MNP (1.5 g)	90	40	91 [31]
2	DSIMHS (0.25mmol)	90	3	94 [32]
3	[Dsim]Cl (10 mol%)	75	180	96 [33]
4	[MIMPS]HSO4 (0.25 mmol)	100	6	93 [34]
5	$[Et_3NH][H_2PO_4]$ (400 mg)	100	300	96 [35]
6	LAIL@MNP (15 mg)	80	30	96 [19]
7	$[(Et_3N)_2SO][HSO_4]_2$, Solvent-free,	120	10	98 (this work)

Reusability of catalyst

The recyclability of $[(Et_3N)_2SO][HSO_4]_2$ are very important characteristic properties for its industrial application. The reusability of the designed catalyst was investigated stirring a mixture of benzaldehyde (1 mmol) and 2-naphthol (2 mmol) in the presence of $[(Et_3N)_2SO][HSO_4]_2$ (15 mol%). At the end of the reaction, $[(Et_3N)_2SO][HSO_4]_2$ was easily separated by simple filtration and washed with hot ethanol and the recovered catalyst was reused for at least five runs without significant degradation in catalytic activity and performance (Figure 4).
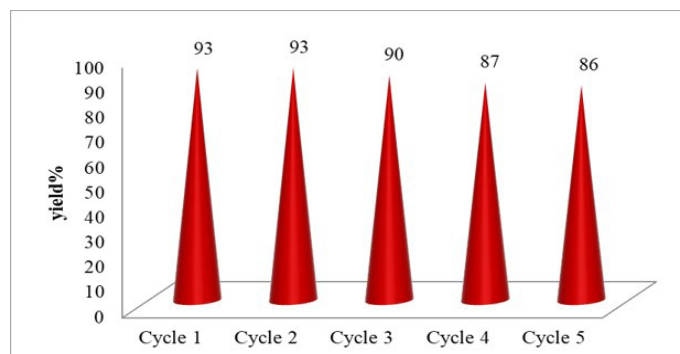

Figure 4: Reusability of $[(Et_3N)_2SO][HSO_4]_2$ in the different reaction cycles of the synthesis of xanthenes derivatives.

The comparisons with other catalytic system reported in the literature indicated the advantages of our protocol in terms of reaction rate and yields of products. The high catalytic efficiency of $[(Et_3N)_2SO][HSO_4]_2$ catalyst may be attributed to abilities of providing hydrogen proton, stabilizing and activating the substrates, which increases the portion of the active sites to react (Table 3).

Concerning the reaction mechanism, we proposed a mechanism (Scheme 4), which supported by the literature [44,45]. Initially 2-naphthol is added to the activated aldehyde and a H_2O molecule is removed from the compound, by helping $[(Et_3N)_2SO][HSO_4]_2$, gives I. Then, intermediate I is activated by the catalyst, and another molecule of 2-naphthol (or dimedone) is added to it to afford II (or III). Intermediate II and III converts to the final products by removal of H_2O.
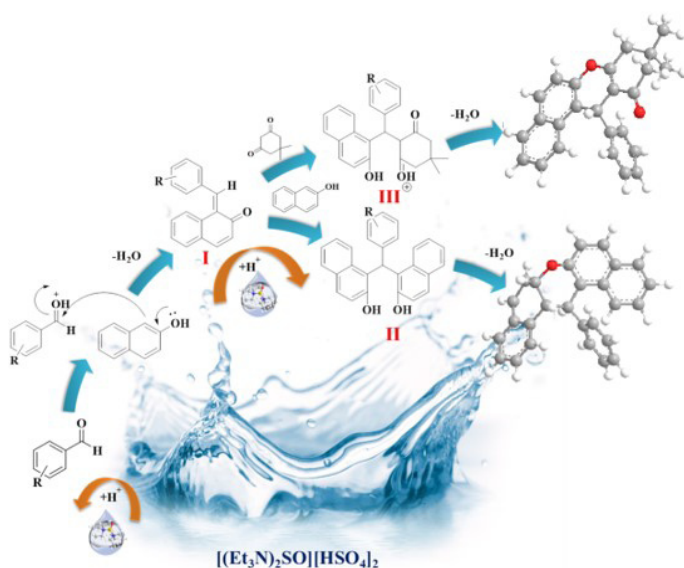
Scheme 4: Proposed mechanism of synthesis of xanthenes derivatives in acidic ionic liquid $[(Et_3N)_2SO][HSO_4]_2$

Conclusion

In summary, a type of novel acidic IL, $[(Et_3N)_2SO][HSO_4]_2$ was synthesized and successfully utilized in the synthesis of tetrahydrobenzo[a]xanthen-11-one and dibenzo[a,j]xanthene derivatives. The catalytic tests revealed that $[(Et_3N)_2SO][HSO_4]_2$ showed significantly more activity among various IL catalysts in the condensation of aldehydes bearing electron-donating or electron-withdrawing groups with 2-naphtol and dimedone. Some advantages of this environmentally safe and benign protocol include a simple reaction set-up, high products yields, short reaction times, and elimination of toxic solvents. The catalyst is inexpensive and readily prepared, and can conveniently be handled and removed from the reaction mixture.

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