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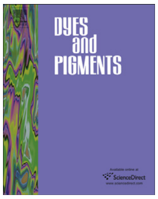

New basic ionic liquid from ethan-1,2-diyl bis (hydrogen sulfate) and DBU (1,8-diazobicyclo[5.4.0]undec-7-ene) as an efficient catalyst for one-pot synthesis of xanthene derivatives

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ABSTRACT

For the first time a new basic ionic liquid from ethan-1,2-diyl-bis (hydrogen sulfate) and 1,8-diazobicyclo [5.4.0]undec-7-ene was suggested. The catalytic activity of the new ionic liquid was tested for synthesis of xanthene derivatives by condensation of aldehydes with *i)* dimedone *ii)* β-naphthol *iii)* 2-hydroxynaphthalene-1,4-dione *iv)* dimedone and β-naphthol *v)* 2-hydroxynaphthalene-1,4-dione and dimedone *vi)* β-naphthol and 2-hydroxynaphthalene-1,4-dione. This approach is a clean, environmentally friendly and convenient work up protocol. The new ionic liquid is an effective and inexpensive catalyst that could easily be recycled and reused five times without significant loss of catalytic activity.

1. Introduction

Multi component reactions (MCRs) are of considerable importance in organic and medicinal chemistry because they have been proved to be remarkably successful in generating molecular complexity in a single synthetic operation [1]. However, great efforts have been and still are being made to find and develop new MCRs.

In recent years, green chemistry has become a major driving force for organic chemists to develop environmentally benign routes to a myriad of materials. Hence, ionic liquids have received recognition as green media in organic synthesis due to their favorable properties, such as negligible vapor pressure, tunable polarity, wide liquid range, good solvating capability, high thermal stability, and case of recyclability [2].

Xanthenes and their derivatives are of considerable interest as they possess a wide range of biological and pharmaceutical properties such as anti-inflammatory [3], activities as well as efficacy in photo dynamic therapy, antiviral, antibacterial, and antagonists for the paralyzing action of zoxazolamine [4]. In addition, they can be used as dyes, pH-sensitive fluorescent material for visualization of bio molecules and utilized in laser technologies [5].

A number of synthetic methods for the synthesis of these compounds have been developed during the past decades [6]. The most commonly used methods involves the condensation of aldehydes with *i)* dimedone *ii)* β-naphthol *iii)* 2-hydroxynaphthalene-1,4-dione *iv)* dimedone and β-naphthol *v)* 2-hydroxynaphthalene-1,4-dione and dimedone *vi)* β-naphthol and 2-hydroxynaphthalene-1,4-dione in the presence of a catalyst [7]. However, these methodologies suffer from one or more disadvantages, such as low yields, tedious workup, strong corrosive and harmful acids, prolonged reaction time, toxic organic solvents, need for excess of the reagents/catalyst, and non-reusability of the catalysts. Therefore, the development of mild, green, inexpensive, non toxic and facile methods for the synthesis of xanthenes derivatives is a necessary part of organic chemistry.

2. Experimental section

2.1. General

Chemicals were obtained from Merck and Sigma–Aldrich. IR spectra were recorded on a Shimadzu 435-U-04 spectrophotometer

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(KBr pellets). ^{1}H NMR spectra were obtained using a Jeol FT NMR 300 MHz spectrometer in $CDCl_3$ or D_2O using TMS as an internal reference. Melting points were determined in open capillary tubes in a Stuart BI Branstead Electrothermal Cat No: IA92003 apparatus and were uncorrected.

2.2. *Preparation of ionic liquid*

2.2.1. *Ethan-1,2-diyl bis (hydrogen sulfate)*

To 12.4 g ethylene glycol (0.2 mol), 46.6 g chlorosulfonic acid (0.4 mol) was added drop wise with good cooling (0–5 °C). After drying in vacuum for 20 min, 43 g (97%) of product were isolated as a pure oily liquid. ^{1}H NMR (300 MHz, D_2O): $\delta = 3.71$ (s, 4H) ppm; Ana. Calcd (%) for $C_2H_6O_8S_2$ (222.19): C, 10.81; H, 2.72; S, 28.86; found: C, 10.62; H, 2.71; S, 28.56.

2.2.2. *Bis-2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepinium-ethyl disulfate [DBU]$_2$[EDS]*

DBU (1,8-diazobicyclo[5.4.0]undec-7-ene) (10.2 g, 0.1 mol) in dichloromethane (10 ml) was added during 10 min to a rapidly stirred solution of ethan-1,2-diyl bis (hydrogen sulfate) (11.1 g, 0.05 mol) in dichloromethane (20 ml) that was cooled in ice bath. Stirring was continued for 15 min, upper layer was separated. After drying in vacuum for 60 min at 70 °C, 15.8 g (98%) was obtained as an oily product. The synthesized ionic liquid was characterized by different methods such as IR, ^{1}H and ^{13}C NMR spectrometer. ^{1}H NMR (300 MHz, D_2O) δ 1.33–1.37 (m, 6H), 1.65 (t, $J = 5.8$ Hz, 2H), 2.26–2.29 (m, 2H), 2.97 (t, $J = 5.7$ Hz, 2H), 3.15–3.23 (m, 4H), 3.30 (s, 2H) ppm; ^{13}C NMR (75 MHz, D_2O): δ 18.2, 22.6, 25.2, 27.7, 32.1, 37.3, 47.5, 53.4, 61.9, 165.2 ppm; IR (KBr disk): 3450–3100, 2980, 1620, 1300, 1170, 1000, 1050, 890, 590 cm^{-1}.

2.3. *General procedure for synthesis of 9-aryl-1,8-dioxo-octhydroxanthenes*

A mixture of cyclic 1,3-dicarbonyl (2 mmol), aldehydes (1 mmol), and [DBU]$_2$[EDS] (40 mol%) was stirred at 120 °C in oil bath for the time show in Table 2. Upon completion of the reaction as indicated by TLC (hexane:ethyl acetate, 8:2), hot EtOH (96%, 1 ml) was added to the mixture which was stirred for 2 min. Then the reaction mixture was poured onto crushed ice and the precipitated solid was collected and recrystallized from ethanol (96%, 3 ml) to afford the pure 9-aryl-1,8-dioxo-octhydroxanthenes derivatives (**2**). Under the same conditions, this approach can be repeated for synthesis of 14-aryl-14H-dibenzo[a,j]xanthenes, 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthene-1,6,10-ones, 14-aryl-14H-dibenzo[a,i]xanthenes-8,13-ones, 13-aryl-5H-dibenzo[b,i]xanthenes-5,7,12,14(13H)-tetraones and 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthene-11-ones.

Table 1
Optimization of reaction conditions for the synthesis of 9-phenyl-1,8-dioxo-octhydroxanthene.

Entry	Catalyst	Conditions	Time (min)	Yield[a] (%)
1	[DBU]$_2$[EDS](40 mol %)	Solvent-Free/100 °C	10	80
2	[DBU]$_2$[EDS] (40 mol %)	Solvent-Free/110 °C	10	85
3	[DBU]$_2$[EDS] (40 mol %)	Solvent-Free/120 °C	5	92
4	[DBU]$_2$[EDS] (40 mol %)	Solvent-Free/130 °C	5	90
5	[DBU]$_2$[EDS] (50 mol %)	Solvent-Free/120 °C	5	89
6	[DBU]$_2$[EDS] (30 mol %)	Solvent-Free/120 °C	10	86
7	[DBU]$_2$[EDS] (20 mol %)	Solvent-Free/120 °C	15	82
8	[EDS] (40 mol %)	Solvent-Free/120 °C	10	60
9	[DBU] (40 mol %)	Solvent-Free/120 °C	10	64[b]
10	–	Solvent-Free/120 °C	10	–

[a] Isolated yields.
[b] 2,2′-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) was major product.

3. Results and discussions

Due to the reasonable needs to clean and green recoverable homogenous catalyst, we synthesized bis-2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepinium-ethyl disulfate [DBU]$_2$[EDS] as a new basic ionic liquid from Ethan-1,2-diyl bis (hydrogen sulfate) and DBU. Firstly, Ethan-1,2-diyl bis (hydrogen sulfate) was prepared by the reaction of ethylene glycol with chlorosulfonic acid in dichloromethane. Finally, the reaction of Ethan-1,2-diyl bis (hydrogen sulfate) with DBU at 0 °C gave bis-2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepinium-ethyl disulfate [DBU]$_2$[EDS] (Scheme 1).

Based on our research interests [8], herein we report an efficient synthesis of 9-aryl-1,8-dioxo-octhydroxanthenes, 14-aryl-14H-dibenzo[a,j]xanthenes, 13-aryl-5H-dibenzo[b,i]xanthenes-5,7,12,14(13H)-tetraones, 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthene-11-ones, 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthene-1,6,10-ones and 14-aryl-14H-dibenzo[a,i]xanthenes-8,13-ones in the presence [DBU]$_2$[EDS] under solvent-free conditions at 120 °C (Scheme 2).

The most suitable reaction conditions for the proposed reaction were achieved by investigating the model reaction of aldehyde (1 mmol), dimedone (2 mmol), and [DBU]$_2$[EDS] (40 mol %). The best result was obtained when the reaction was carried at 120 °C in the absence of any solvent. As shown in Table 1, increasing temperature up to 120 °C can result in improving the yields (entries 1–3). And, decreasing in yield at 130 °C (entry 4), may be related to decomposition of respective IL. By comparing entries 3 and 5–7 at 120 °C in Table 1, we recognized that the 40 mol % of IL was optimum amount for this reaction. Using [EDS] as a catalyst in the reaction caused low yields (entry 8) and in absence of any IL, no reaction occurred (entry 10). Also, when DBU was used as catalyst, 2,2′-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) was the major product.

Subsequently, reactions of variously substituted aromatic aldehydes with 2 equivalent of dimedone (A) were carried out under the most suitable reaction condition (Table 2, entries 1–10). In all cases studied, the reaction proceeded smoothly to give the corresponding 9-aryl-1,8-dioxo-octhydroxanthene derivatives in satisfactory yields. Most importantly, aromatic aldehydes with substituents bearing electron-donating or electron-withdrawing groups reacted successfully in the presence of [DBU]$_2$[EDS] as catalyst.

The protocol was further extended by exploring with 2 equivalent of β-naphthol (B) and aromatic aldehydes (entries 11–15). As shown in Table 2, aldehydes with electron-withdrawing groups disappeared faster by producing high yield products in short time. Similarly, reaction of 2 equivalent of 2-hydroxynaphthalene-1,4-dione (C) and different substituted aromatic aldehydes under the above optimized reaction condition proceeded smoothly to afford the corresponding 13-aryl-5H-dibenzo[b,i]xanthenes-5,7,12,14(13H)-tetraones (entries 16–20).

The scope of this reaction was extended by replacing one equivalent of β-naphthol (B) with dimedone (A). It was also observed that in the presence of IL (40 mol%) high yields of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthene-11-ones were resulted (entries 21–25).

In continuation, by using dimedone (A) and 2-hydroxynaphthalene-1,4-dione (C) with aromatic aldehydes, corresponding 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthene-1,6,10-ones obtained within 5–9 min with high yields (entries 26–29). And finally, we completed our study using one equivalent of β-naphthol (B), 2-