

Synthesis of 1,8-Dioxo-octahydroxanthenes Catalyzed by Acidic Ionic Liquids in Aqueous Media

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Abstract Some halogen-free acyclic task-specific ionic liquids (TSILs) were synthesized as cheap and recyclable catalysts for synthesis of 1,8-dioxo-octahydroxanthenes in water. This methodology offers several advantages, such as good yields, short reaction times, simple procedure, and mild conditions. The products could simply be separated from the catalyst/water, and the catalyst could be reused at least six times without noticeably decreasing the catalytic activity.

Keywords 1,8-Dioxo-octahydroxanthenes · Ionic liquid · Catalyst

1 Introduction

Xanthene derivatives are important classes of organic compounds of a large number of naturally occurring, as well as synthetic derivatives, and occupy a prominent position in medicinal chemistry [1]. Xanthene-based compounds have also been investigated for agricultural bactericide activity [2], anti-inflammatory effect [3] and antiviral activity [4]. In particularly, xanthenediones constitute a structural unit in a number of natural products [5],

and have been used as versatile synthons because of the inherent reactivity of the inbuilt pyran ring [6]. The synthesis of xanthenediones usually condenses appropriate active methylene carbonyl compounds with aldehydes catalyzed mainly by organic and mineral acids, which often suffer from the drawbacks of long reaction times, harsh reaction conditions, toxicity, and difficulty in product separation.

Recently, many synthetic methods for preparing xanthenediones compounds have been reported by the condensation of aromatic aldehydes and active methylene carbonyl compounds in the presence of *p*-dodecylbenzene-sulphonic acid [7], *p*-toluenesulfonic acid [8], Fe³⁺-montmorillonite [9], NaHSO₄-SiO₂ or silica chloride [10], Amberlyst-15 [11], silica sulfuric acid [12], (NH₄)₂HPO₄ [13], Dowex-50 W [14], SbCl₃/SiO₂ [15], cyanuric chloride [16], and BiCl₃ [17] as catalysts, as well as with the assistance of microwave [18] or ultrasound irradiation [19, 20]. However, the search for the new readily available and green catalysts is still being actively pursued.

Ionic liquids have attracted extensive interest as excellent alternatives to organic solvents these years, due to their favorable properties. Brønsted-acidic TSILs, which possess the advantageous characteristics of solid acids and mineral acids, are designed to replace traditional mineral liquid acids, such as sulfuric acid and hydrochloric acid. The use of ionic liquids as reaction medium may offer a convenient solution to both the solvent emission and catalytic recycling problem. Some researchers have already used ionic liquids as solvents/catalysts to synthesis xanthenediones compounds. Fan et al. used InCl₃ · 4H₂O [21] and Wang et al. used NaHSO₄ for the condensation of aromatic aldehydes with 1,3-cyclohexanedione in ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF₄) [22]. Dabiri

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et al. [23] used acidic ionic liquid 1-methylimidazolium trifluoroacetate ([Hmim]TFA) as an efficient reusable catalyst for the synthesis of 1,8-dioxo-octahydroxanthenes and 1,8-dioxo-decahydroacridines. Srinivasan et al. reported an efficient method promoted by acidic ionic liquid [Hbim]BF₄ under ultrasound irradiation. In fact, the use of Brønsted-acidic TSILs as catalysts is an area of ongoing activity; however, the development and exploration of Brønsted-acidic TSILs are currently in the preliminary stage. To date, research of some “greener” halogen-free ionic liquids with phosphate or octyl sulfate anions and the effects of the anion and toxicology have appeared in literature [24–26]. Thus, it is necessary to synthesize less expensive and halogen-free TSILs, which can be used straightforwardly with the simple procedure.

In our previous work some novel and cheap SO₃H-functional halogen-free acidic ionic liquids that bear an alkane sulfonic acid group in an acyclic trialkylammonium cation have been synthesized to catalyze some organic reactions [27–30]. In continuation of our work in studying acid-catalyzed reactions in ionic liquids, we report here the synthesis of 1,8-dioxo-octahydroxanthenes via condensation of aldehydes and 1,3-cyclohexanedione in these halogen-free acidic ionic liquids.

2 Experimental

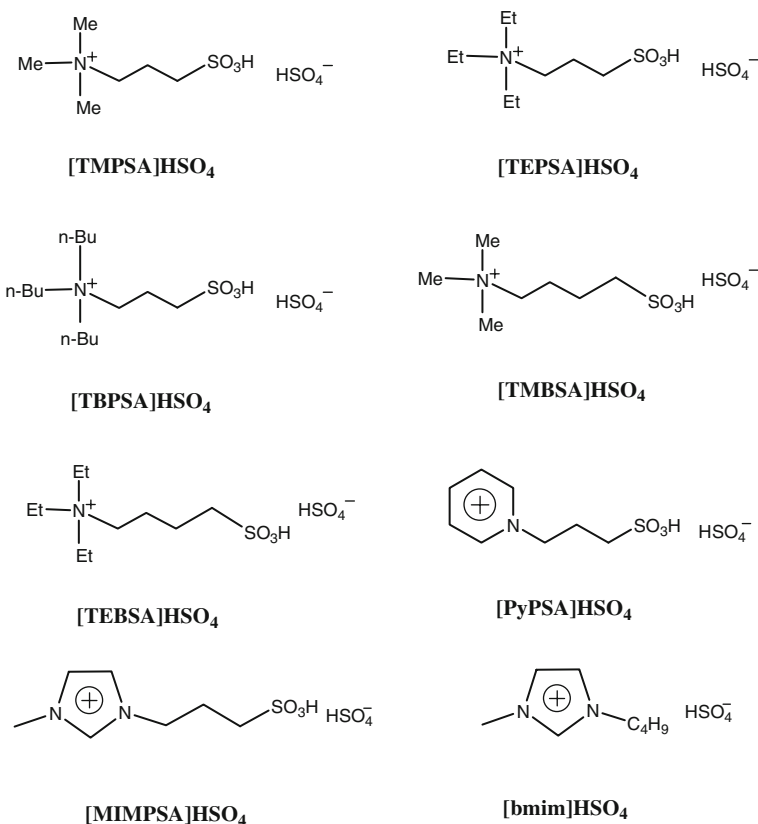
2.1 Materials and Methods

Melting points were determined on X-6 microscope melting apparatus and reported uncorrected. The IR spectra were run on a Nicolette spectrometer and expressed in cm⁻¹ (KBr). ¹H NMR spectra were recorded on Bruker DRX300 (300 MHz) and ¹³C NMR spectra on Bruker DRX300 (75.5 MHz) spectrometer. Elemental analyses were recorded on Perkin Elmer C spectrometer. Mass spectra were obtained with automated FININIGAN Trace Ultra-Trace DSQ GC/MS spectrometer. All chemicals (AR grade) were commercially available and used without further purification.

2.2 Synthesis of Acidic Halogen-Free Acidic Ionic Liquids (TSILs)

All acyclic SO₃H-functionalized halogen-free acidic ionic liquids such as [TMPSA]HSO₄, [TMBSA]HSO₄, were synthesized according to our previous methods [27–30], the pyridine, imidazole-based acidic ionic liquids for comparison were according to reported methods [31]. Their structures were analyzed by ¹HNMR, ¹³CNMR and MS spectral data (Scheme 1).

Scheme 1 Structures of the TSILs used in condensation reaction 1 2 3



The selected spectral data for acidic halogen-free TSILs:

N, N, N-trimethyl-*N*-propanesulfonic acid ammonium hydrogen sulfate [TMPSA]HSO₄ ¹H NMR (300 MHz, D₂O): δ 3.22 (*t*, *J* = 7.2 Hz, 2H, N-CH₂-C-C-SO₃), 2.90 (*s*, 9H, N-CH₃), 2.73 (*t*, *J* = 7.8 Hz, 2H, N-C-C-CH₂-SO₃), 1.99 (*m*, 2H, N-C-CH₂-C-SO₃). ¹³C NMR (75.5 MHz, D₂O): δ 65.00, 52.51, 47.89, 18.85. MS (*m/z*): 279.05 (*M*⁺), 182.14(100).

N, N, N-trimethyl-*N*-butanesulfonic acid ammonium hydrogen sulfate [TMBSA]HSO₄ ¹H NMR (300 MHz, D₂O): δ 3.24 (*t*, *J* = 8.4 Hz, 2H, N-CH₂-C-C-C-SO₃), 2.99 (*s*, 9H, N-CH₃), 2.85 (*t*, *J* = 7.5 Hz, 2H, N-C-C-C-CH₂-SO₃), 1.82 (*m*, 2H, N-C-CH₂-C-C-SO₃), 1.70 (*m*, 2H, N-C-C-CH₂-C-SO₃). ¹³C NMR (75.5 MHz, D₂O): δ 66.15, 53.16, 50.31, 21.46, 19.93. MS (*m/z*): 293.36 (*M*⁺), 196.39(100).

N-propanesulfonic acid pyridinium hydrogen sulfate [PyPSA]HSO₄ ¹H NMR (300 MHz, D₂O): δ 8.62 (*d*, *J* = 6.0 Hz, 2H, H-2, H-6), 8.30 (*t*, *J* = 7.8 Hz, 1H, H-4), 7.84 (*t*, *J* = 6.9 Hz, 2H, H-3, H-5), 4.51 (*t*, *J* = 7.5 Hz, 2H, N-CH₂-C-C-SO₃), 2.73 (*t*, *J* = 7.2 Hz, 2H, N-C-C-C-CH₂-SO₃), 2.18–2.23 (*m*, 2H, N-C-CH₂-C-SO₃). ¹³C NMR (75.5 MHz, D₂O): δ 146.35, 144.70, 128.82, 60.28, 47.48, 26.47.

1-methyl-3-propanesulfonic acid imidazolium hydrogen sulfate [MIMPSA]HSO₄ ¹H NMR (300 MHz, D₂O): δ 8.47(*s*, 1H, CH), 7.24(*d*, *J* = 1.5 Hz, 1H, CH), 7.17(*d*, *J* = 1.5 Hz, 1H, CH), 4.08(*t*, *J* = 6.9 Hz, 2H, N-CH₂-C-C-SO₃), 3.62(*s*, 3H, N-CH₃), 2.64(*t*, 2H, *J* = 7.5 Hz, 2H, N-C-C-CH₂-SO₃), 2.03 (*m*, 2H, N-C-CH₂-C-SO₃). ¹³C NMR (75.5 MHz, D₂O): δ 136.53, 124.32, 122.57, 48.13, 47.66, 36.46, 25.48. MS (*m/z*): 302.0 (*M*⁺), 300.93(100).

1-butyl-3-methylimidazolium hydrogen sulfate [bmim]HSO₄ ¹H NMR (300 MHz, D₂O): δ 8.62 (*s*, 1H, H-2), 7.33–7.38 (*m*, 2H, H-4, H-5), 4.09 (*t*, 2H, *J* = 7.1 Hz), 3.79 (*s*, 3H), 1.68–1.78 (*m*, 2H), 1.16–1.24 (*m*, 2H), 0.79 (*t*, 3H, *J* = 7.4 Hz). ¹³C NMR (75.5 MHz, D₂O): δ 136.35, 124.07, 122.80, 49.85, 36.33, 31.80, 19.31, 13.25. *m/z*: 236(*M*⁺), 139(100, *M*⁺-HSO₄).

2.3 General Procedure for the Synthesis of 1,8-Dioxo-octahydroxanthenes

To a round-bottomed flask charged with aldehyde (5 mmol) **1**, 5,5-dimethyl-1,3-cyclohexanedione (dimedone) or

1,3-cyclohexanedione (10 mmol) **2** in 5 mL of water was added acidic ionic liquid (0.5 mmol) under stirring. The mixture was then stirred for a certain time at 100 °C (Scheme. 2). On completion (monitored by TLC), the precipitated crude product was collected by filtration and recrystallized from ethanol (95%) to afford pure 1,8-dioxo-octahydroxanthenes **3**. The filtrate containing ionic liquid could be reused directly in the next run without further purification. The products were identified by IR, ¹H NMR, and physical data (*m.p.*) with those reported in the literatures.

3 Results and Discussion

The synthesis procedures of SO₃H-functionalized halogen-free acidic ionic liquids were made up of two-step atom-economic reaction. The zwitterionic-type precursors were prepared through a one-step direct sulfonation reaction. The zwitterions acidification was accomplished by mixing of

Table 1 Synthesis of 1,8-dioxo-octahydroxanthenes catalyzed by acidic ionic liquids^a

Entry	Catalyst	TSILs (mol%) ^b	T (°C)	Time (h)	Yields (%) ^c
1	–	–	100	6.0	–
2	[TMPSA] · HSO ₄	4	100	6.0	90
3	[TMPSA] · HSO ₄	6	100	4.5	92
4	[TMPSA] · HSO ₄	8	100	1.5	92
5	[TMPSA] · HSO ₄	10	100	1.0	94
6	[TMPSA] · HSO ₄	12	100	1.0	94
7	[TMPSA] · HSO ₄	15	100	1.0	94
8	[TMPSA] · HSO ₄	10	90	2.5	93
9	[TMPSA] · HSO ₄	10	80	3.0	90
10	[TEPSA] · HSO ₄	10	100	1.0	90
11	[TBPSA] · HSO ₄	10	100	1.0	92
12	[TMBSA] · HSO ₄	10	100	1.0	94
13	[TEBSA] · HSO ₄	10	100	1.0	93
14	[PyPSA] · HSO ₄	10	100	1.0	91
15	[MIMPSA] · HSO ₄	10	100	1.0	92
16	[bmim] · HSO ₄	10	100	1.5	90

^a 5 mmol benzaldehyde, 10 mmol dimedone, water is used as a solvent

^b Molar ration of TSILs to benzaldehyde

^c Isolated yields

Scheme 2 Synthesis of xanthenedione derivatives catalyzed by the TSILs

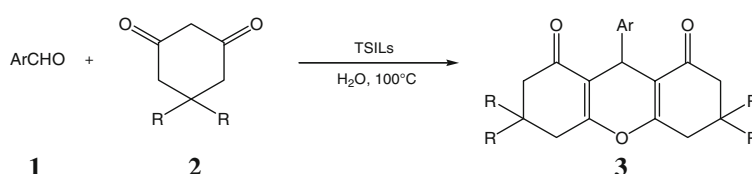


Table 2 Reusing of the ionic liquid [TMPSA] · HSO₄^a

Entry	Run	Isolated yield (%)
1	Fresh	94
2	1	92
3	2	90
4	3	91
5	4	91
6	5	90
7	6	89

^a 5 mmol benzaldehyde, 10 mmol dimedone, 0.5 mmol catalyst, 100 °C, 1.0 h

zwitterions with sulfuric acid (98%, aq.) to convert the pendant sulfonate group into SO₃H-functionalized halogen-free acidic ionic liquids. The chemical yields for both the zwitterions formation and acidification steps were essentially quantitative since neither reaction produced byproducts. The preparation of [bmim]HSO₄ was accomplished by anion metathesis with NaHSO₄ in good yield of 96%.

The fresh new TSILs with HSO₄[−] anion are somewhat viscous colorless liquids at room temperature. All produced TSILs are entirely miscible with water and soluble or partly soluble in organic solvents.

To optimize the reaction conditions, for the beginning of this study, benzaldehyde and dimedone were employed as the model reactants at 100 °C in TSILs for a length of time to compare the catalytic performance of the TSILs (Table 1). As shown in Table 1, no desirable product could

be detected when a mixture of benzaldehyde and dimedone was heated at 100 °C for 6 h in the absence of ionic liquid (Table 1, entry 1), which indicated that the catalysts should be absolutely necessary for this condensation. All the eight TSILs proved to be very active, leading to 90–94% yield of 1,8-dioxo-octahydroxanthenes in the presence of 10% TSILs (entries 5, 8–16). In addition, ionic liquids containing the shorter length of alkyl chain are relatively cheaper. Further, the better immiscibility of the resulted product with the shorter length of alkyl chain ionic liquids should facilitate the separation in work-up procedure. Hence, [TMPSA]HSO₄ should be the best catalyst for this condensation among these ionic liquids and the optimized reaction conditions went to entry 5 in Table 1.

Condensation reaction in [TMPSA]HSO₄/H₂O gave a yield of 94%, which was nearly the same as that in organic solvents. The chemical industry is under considerable pressure to replace many of the volatile organic compounds (VOCs) that are currently used as solvents in organic synthesis. As a clean and cheap solvent, it is important to carry out this reaction in water for the environmental and economic reasons.

When optimizing the reaction condition, the recycling performance of [TMPSA] · HSO₄ was investigated using the above same model reaction. After the separation of the products, the catalyst-containing filtrate was reused in the next run without further purification. The data listed in Table 2 showed that the [TMPSA] · HSO₄ could be reused at least six times without obviously decreasing of the catalytic activity. Compared with the traditional solvents and catalysts, the easy recycling performance is also an

Table 3 Synthesis of 1,8-dioxo-octahydroxanthenes catalyzed by [TMPSA] · HSO₄^a

Entry	Ar	R	Product	Time (h)	mp (°C)[Lit]	Yields (%) ^b
1	C ₆ H ₅	CH ₃	3a	1.0	198–200[9]	94
2	<i>p</i> -FC ₆ H ₄	CH ₃	3b	1.0	223–225[18]	92
3	<i>o</i> -ClC ₆ H ₄	CH ₃	3c	1.0	226–228[9]	95
4	<i>p</i> -ClC ₆ H ₄	CH ₃	3d	1.0	230–232[9]	92
5	<i>p</i> -BrC ₆ H ₄	CH ₃	3e	1.5	231–233[18]	86
6	<i>m</i> -NO ₂ C ₆ H ₄	CH ₃	3f	1.0	146–117[18]	91
7	<i>p</i> -NO ₂ C ₆ H ₄	CH ₃	3g	1.0	221–223[9]	95
8	<i>p</i> -CH ₃ C ₆ H ₄	CH ₃	3h	1.5	212–214[9]	92
9	<i>p</i> -CH ₃ OC ₆ H ₄	CH ₃	3i	2.0	235–237[9]	93
10	<i>p</i> -HOC ₆ H ₄	CH ₃	3j	1.0	245–247[9]	93
11	C ₆ H ₅	H	3k	1.0	267–269[16]	89
12	<i>p</i> -FC ₆ H ₄	H	3l	1.0	275–277[16]	90
13	<i>o</i> -ClC ₆ H ₄	H	3m	1.0	248–250[16]	88
14	<i>p</i> -ClC ₆ H ₄	H	3n	1.0	286–288[16]	90
15	<i>p</i> -BrC ₆ H ₄	H	3o	1.5	284–286[16]	91
16	<i>m</i> -NO ₂ C ₆ H ₄	H	3p	1.0	285–287[16]	92
17	<i>p</i> -NO ₂ C ₆ H ₄	H	3q	1.0	262–264[16]	91
18	<i>p</i> -CH ₃ OC ₆ H ₄	H	3r	1.0	200–202[16]	92

^a 5 mmol benzaldehyde, 10 mmol dimedone or 1,3-cyclohexanedione, 0.5 mmol catalyst, 100 °C

^b Isolated yields

attractive property of the ionic liquids for the environmental protection and economic reasons.

Then, the condensation reaction of various aldehydes with dimedone or 1,3-cyclohexanedione in the presence of [TMPSA] · HSO₄ as an environmentally benign ionic liquid was explored under the optimized reaction conditions described above and the results are presented in Table 3. It can easily be seen that *t* in all cases the reactions gave the products in good yields ranged from 88–95%. Aromatic aldehydes carrying either electron-donation or electron-withdrawing substituents afforded good yields of 1,8-dioxo-octahydroxanthenes in high purity.

4 Conclusion

In summary, some acyclic Brønsted-acidic task-specific ionic liquids such as [TMPSA] · HSO₄, [TMBSA] · HSO₄ etc. were synthesized in an atom-economic procedure. These ionic liquids were found to be efficient catalysts for synthesis of 1,8-dioxo-octahydroxanthenes in aqueous media, offering the practical convenience in the product separation from the ionic liquid system. The merit of this methodology is that it is simple, mild, and efficient. And the raw materials are cheaper than TSILs with imidazole or triphenylphosphine as the cation. Therefore, we believe that the work reported here would have potential application in green chemistry.

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