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An Efficient Green Synthesis of Xanthenedione Derivatives Promoted by Acidic Ionic Liquid

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ABSTRACT: *Xanthenedione derivatives were prepared through the condensation reaction of aromatic aldehydes with 5,5-dimethyl-1,3-cyclohexanedione promoted by acidic ionic liquid. The reaction time was 20–40 min with the yields between 82.3% and 95.3%. It was shown that the proposed method was fast, high efficient, and environmentally benign.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:609–611, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20486

INTRODUCTION

Room temperature ionic liquids (RTILs) have received increasingly attention as potential "greener" alternatives to volatile organic solvent, and they have been investigated extensively as a solvent or catalyst for many important organic reactions because of their special properties such as their negligible vapor pressure, tunable polarity, high thermal stability, good solvating ability, ease of recyclability, and their potential to enhance reaction rates and selectivity [1]. They have also been referred as "designer solvents," as their properties can be altered by the fine-tuning of parameters such as the choice of organic cation, inorganic anion, and alkyl chain attached to the organic cation. These structural variations offer flexibility to the chemist to devise the most idealized solvent and catalyst, catering for the needs of a particular process [2].

Xanthenedione derivatives have attracted considerable attention owing to their unique biological activity, and they were valuable intermediates because of the inherent activity of the inbuilt pyran ring [3]. The conventional synthetic methods of xanthenedione derivatives were carried out in organic solvent [4]. As an improvement, the condensation reaction of aromatic aldehydes with 5,5-dimethyl-1,3-cyclohexanedione was proceeded in water for 6 h, using NH_2SO_3H and SDS as catalyst [5]. Microwave irradiation has also been used to promote the condensation reaction [6]. Very recently, Fan et al. reported that the synthesis of xanthenedione derivatives could be proceeded in ionic liquid [bmim]BF_4 catalyzed by Lewis acid $InCl_3$ [7] and $FeCl_3{\cdot}6H_2O$ [8], respectively, the reaction time was between 4 and 10 h. However, some of these methods have not been entirely satisfactory, associating with disadvantages such as longer reaction time, using volatile and toxic organic solvent, using catalyst that cannot be recycled, and so on.

In continuing our endeavor in green synthesis and using ionic liquids as a recyclable, eco-friendly reaction medium to enhance rates and selectivity [9], herein, we report a condensation reaction of cyclohexanedione derivatives with aromatic aldehydes (Scheme 1), which could efficiently proceed in task-specific acidic ionic liquid without any other

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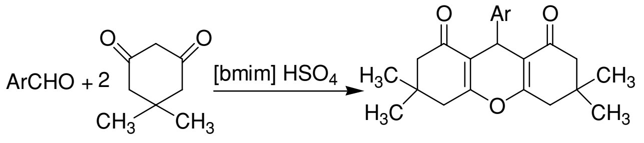


1 **2** **3**

SCHEME 1

catalyst. The reaction time in this method was considerably reduced compared with those in the documented methods [5,7,8].

RESULTS AND DISCUSSION

In our initial research, 4-chlorobenzaldehyde was selected as a representative reactant to optimize the reaction conditions. As shown in Table 1, the reaction could proceed efficiently in acidic ionic liquids [hmim]HSO_4, [emim]HSO_4, and [bmim]HSO_4 (entries 1–3). However, only moderate yield of **3b** (3,3,6,6-tetramethyl-9-(4-chlorobenzyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydro-xanthene) could be obtained when [bmim]H_2PO_4 was employed (entry 4). Attempts to perform the reaction in [bmim]Br, [bmim]BF_4, and [bmim]PF_6 (entries 5–7) were failed, even at prolonged reaction time. These results suggested that the used ionic liquids play the dual role of acidic catalyst and solvent. Moreover, the catalytic activity of the ionic liquids was dependent heavily upon the Brönsted acidity of the counteranion. The catalytic performance of the ionic liquids with hydrogen sulfate counteranion was much better than that of the other employed ionic liquids under the same reaction conditions. Probably, this was due to the high Brönsted acidity of hydrogen sulfate counteranion. According to the literature, the Hammett function (H_0) of [bmim]HSO_4 and [bmim]H_2PO_4 was 0.73 and 2.55, respectively [10]. The catalytic performances of [emim]HSO_4, [bmim]HSO_4, and [hmim]HSO_4 were similar, indicating the low impact of the cation of the ionic liquids on the catalytic activity. [bmim]HSO_4 was chosen for the further study in this work.

Effects of reaction temperature on the yields of the products were studied by performing the condensation reaction at room temperature, 80°C, and 100°C, respectively (entries 3, 8, 9). The results show that the higher reaction temperature, the more efficiently the reaction could proceed.

A variety of substituted aromatic aldehydes were subjected to the condensation reaction to study the substituted effects on their reactivity. The results are summarized in Table 2. For most of the substrates, the reaction could be completed in 20–40 min with high yields, with the substrates having either electron-donating groups or electron-withdrawing groups. However, when the aromatic aldehydes had a bigger ortho-position substituent, such as 2-nitrobenzaldehyde and 2,4-dinitrobenzaldehyde, the reaction could not take place owing to the stereoeffect. 9-Anthraldehyde and acetophenone either could not react with **2** under the above conditions.

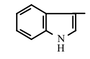
The reusability and recycling of [bmim]HSO_4 was also investigated. For the condensation reaction of 4-chlorobenzaldehyde and 5,5-dimethylcyclohexanedione, the product was separated by directly filtering from the reaction mixture. The extract was dried under vacuum at 90°C for 2 h to eliminate any water. The recycled [bmim]HSO_4 was reused for subsequent reactions. The catalytic activity of [bmim]HSO_4 did not show any significant decrease even after five runs.

TABLE 1 Condensation Reactions of 4-Cholorobenzenaldehyde and 5,5-Dimethyl-1,3-cyclo-hexane Dione in Different Ionic Liquids[a]

Entry	*RTILs*	*T (°C)*	*Time (min)*	*Yield (%)*[b]
1	[Hmim]HSO_4	80	30	85
2	[Emim]HSO_4	80	30	83
3	[Bmim]HSO_4	80	30	86
4	[Bmim]H_2PO_4	80	30	46
5	[Bmim]Br	80	60	Trace
6	[Bmim]BF_4	80	60	Trace
7	[Bmim]PF_6	80	60	Trace
8	[Bmim]HSO_4	r.t.	30	27
9	[Bmim]HSO_4	100	30	95

[a] Reaction conditions: 1 mmol 4-chlorobenzaldehyde, 2 mmol 5,5-dimethyl-1,3-cyclo-hexanedione, 1 mL ionic liquid.
[b] Isolated yields.

TABLE 2 Synthesis of Xanthenedione Derivatives in Acidic Ionic Liquid [bmim]HSO_4

Entry	*Ar*	*Time (min)*	*Yield (%)*
3a	4-$(CH_3)_2NC_6H_4$	35	88
3b	4-ClC_6H_4	20	95
3c	2-ClC_6H_4	20	94
3d	4-HOC_6H_4	25	94
3e	4-$CH_3OC_6H_4$	20	95
3f	3,4-$(OCH_2O)C_6H_3$	30	93
3g	C_6H_5	25	93
3h	4-BrC_6H_4	25	90
3i	4-$CH_3C_6H_4$-	20	89
3j	3-$NO_2C_6H_4$	40	83
3k	$C_6H_5CH{=}CH$	30	90
3l	4-HO-3-$CH_3OC_6H_3$	25	92
3m		30	82

EXPERIMENTAL

Melting points were recorded on an electrothermal apparatus and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were determined with a Brucker AVANCE 400 spectrometer ($CDCl_3$), using TMS as an internal standard. IR spectra (cm^{-1}) were measured with a BIO-RAD FTS3000 spectrometer. RTILs employed in the work were prepared according to the literature [11].

General Procedure

In a typical procedure, aromatic aldehydes **1** (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione **2** (2 mmol) and [bmim]HSO_4 (1 mL) were stirred at 100°C for a certain period of time to complete the reaction (monitored by TLC). The products were separated by filtering and washed with water. The obtained solid was recrystallized from 80% ethanol. Then, the desired products 3,3,6,6-tetramethyl-9-aryl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene **3a–m** were obtained. All the products were fully characterized by IR, ^{1}H NMR, and elemental analysis.

Spectral Data for Compound **3m:** mp 256–257°C. ^{1}H NMR ($CDCl_3$) δ: 0.92 (s, 6H), 1.11 (s, 6H), 2.13–2.26 (m, 4H), 2.47–2.57 (m, 4H), 5.12 (s, 1H), 7.03–7.41 (m, 5H), 8.16 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 24.07, 27.94, 29.50, 32.49, 41.20, 51.24, 111.79, 115.03, 117.83, 118.97, 119.45, 121.48, 124.42, 126.15, 136.87, 162.37; IR (KBr): 3357.5, 3058.6, 2956.3, 2869.6, 1668.1, 1660.4, 1614.1, 1454.1, 1359.6, 1195.7, 1164.8, 1135.9, 734.8; Anal. Calcd. for $C_{25}H_{27}O_3$ N: C, 77.09; H, 6.99; N, 3.60. Found: C, 77.11; H, 6.95; N, 3.67.

CONCLUSIONS

The present synthetic method is a simple and efficient green synthesis of 3,3,6,6-tetramethyl-9-aryl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene derivatives. The method offers marked improvements with regard to operational simplicity, reaction time, general applicability, high yields of products, and greenness of procedure, and can avoid the use of the hazardous organic solvents and toxic catalysts. It provides a practical alternative to the existing procedures. The application studies of the task-specific ionic liquids for other reactions are in progress.

SUPPLEMENTARY INFORMATION

Analytical data of different compounds are available as supplementary material from the author on request (wangc69@yahoo.com.cn).

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