

CONDENSATION OF 1,3-CYCLOHEXANEDIONE WITH AROMATIC ALDEHYDES CATALYZED BY ACIDIC IONIC LIQUIDS

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Abstract : An efficient and convenient approach to the synthesis of 9-aryl-2, 3, 4, 5, 6, 7-hexahydro-2H-Xanthene-1, 8-dione by condensation of 1, 3-cyclohexanedione with aromatic aldehydes catalyzed by acid ionic liquid 1- methylimidazolium hydrogen sulphate ([Hmim]HSO₄) is described. This method provides many advantages such as being environmentally benign, simple work-up, short reaction times, obtaining in good to excellent yields with high purity, and the reusability of ionic liquids.

Introduction

Xanthenedione derivatives have attracted considerable interests in recent years, since they constitute a structural unit in a number of natural products and have been used as versatile synthons because of the inherent reactivity of the inbuilt pyran ring.¹⁻² Usually, Xanthenedione derivatives can be obtained through the acid or base catalyzed condensation of appropriate active methylene carbonyl compounds with aldehydes.¹ It was reported 9-aryl-2,3,4,5,6,7-hexahydro-2H-xanthene-1,8-dione derivatives could be obtained by condensation of 1, 3-cyclohexanedione derivatives with aromatic aldehydes catalyzed by 4-toluenesulfonic acid,³ TiO₂/SO₄²⁻,⁴ acidic resin amberlyst-15,⁵ polyaniline-p-toluenesulfonate salt,⁶ phase transfer catalysts,⁷ or facilitated by MW irradiation⁸ and ultrasound.⁹ while these procedures are usually restricted by long reaction times, using volatile toxic organic solvents, and sometimes only moderate yields obtained. Recently, some literatures reported ionic liquid 1-n-butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF₄) could be used as a green reaction medium, using FeCl₃·6H₂O,¹⁰ InCl₃·4H₂O¹¹ or NaHSO₄¹² as catalyst respectively. In continuation of our interest in using ionic liquids as eco-friendly medium and catalyst for the condensation reactions,¹³ we report herein 1, 3-cyclo-hexanedione could be reacted with aromatic aldehydes smoothly in acid ionic liquid [Hmim]HSO₄ without any added catalyst.

Results and discussion

Firstly, we examined the efficacy of different ionic liquids (Fig. 1) in the reaction of 4-methoxyl-benzaldehyde with 1,3-cyclohexanedione. The results were listed in Table 1. We found that all the investigated acid ionic liquids showed more efficient catalytic activity compared with [Bmim]BF₄ and ethylammonium nitrate (EAN). Obviously, [Hmim]HSO₄ showed the best result, which play a dual role as solvent and promoter in this reaction. So we selected the [Hmim]HSO₄ as reaction medium in the following reactions.

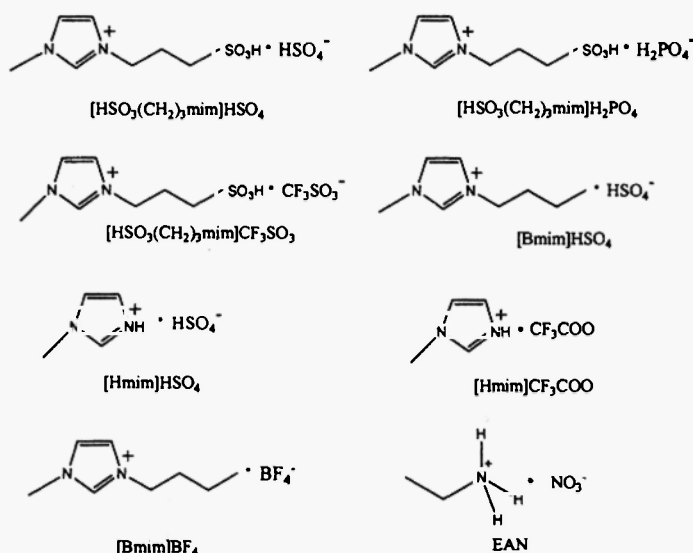
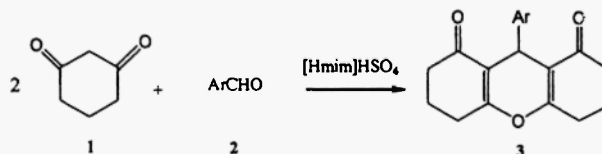


Fig. 1 Structure of ionic liquids

Table-1 : Condensation of 4-methoxybenzaldehyde with 1,3-cyclohexanedione in different ionic liquids

Entry ^a	Ionic liquids (IL)	Yield (%) ^b
1	[HSO ₃ (CH ₂) ₃ mim]HSO ₄	84
2	[HSO ₃ (CH ₂) ₃ mim]H ₂ PO ₄	88
3	[HSO ₃ (CH ₂) ₃ mim]CF ₃ SO ₃	71
4	[Bmim]HSO ₄	67
5	[Hmim]CF ₃ COO	86
6	[Hmim]HSO ₄	93
7	EAN	61
8	[Bmim]BF ₄	13

^a All reactions were run with 4-methoxybenzaldehyde (1mmol) and 1,3-cyclohexanedione (2mmol) in ionic liquid (2ml) at 80°C for 4 hours. ^b Isolated yields.

**Scheme 1**

Subsequently, the scope of the condensation of 1, 3-cyclohexanedione 1 and a variety of aromatic aldehydes 2 in ionic liquid [Hmim]HSO₄ was investigated (Scheme 1). The results were summarized in Table 2. All the products were characterized by IR, ¹H NMR, and melting points which were consistent with the literature data. As can be seen from Table 2, this procedure was found to be general and applicable to the

aromatic aldehydes bearing various substituents such as halide, nitro, methoxyl, hydroxyl, etc. The aromatic aldehydes bearing electron--withdrawing groups reacted more easily compared with those containing electron-donating groups. It is noteworthy that the aromatic α,β -unsaturated aldehyde, Cinnamic aldehyde (Entry 13) could be completed in one hour under reaction condition with high yield obtained. Disappointedly, we couldn't obtain satisfactory results when applied to aliphatic aldehydes under the same reaction conditions, as is the same as the literature.³ Moreover, the ionic liquid could be typically recovered and reused with no appreciable decrease in yields and reaction rates (Entry 14).

Table-2 : Condensation of 1, 3-cyclohexanedione with aromatic aldehydes in [Hmim]HSO₄^a

Entry	Ar	Product	Time/h	Yield /% ^b	Mp/°C ^c	Lit. Mp/°C
1	C ₆ H ₅	3a	2	82	267-268	270-271 ⁸
2	4-CH ₃ O C ₆ H ₄	3b	4	93	206-207	204-206 ¹²
3	4-Cl C ₆ H ₄	3c	2	92	289-290	289-291 ⁸
4	4-Br C ₆ H ₄	3d	2	93	284-285	285-286 ⁸
5	4-NO ₂ C ₆ H ₄	3e	2	93	265-267	265-266 ⁸
6	3-OH C ₆ H ₄	3f	2	89	255-257	257 ¹⁴
7	3-NO ₂ C ₆ H ₄	3g	2	78	282-284	286-288 ⁸
8	2-OH C ₆ H ₄	3h	3	88	230-231	233 ¹⁴
9	2-Cl C ₆ H ₄	3i	3	85	250-251	250-251 ⁸
10	3-OCH ₃ -4-OH C ₆ H ₃	3j	4	87	238-239	242-243 ¹²
11	3,4-Cl ₂ C ₆ H ₃	3k	3	76	232-234	231-232 ⁸
12	2,4-Cl ₂ C ₆ H ₃	3l	3	74	230-231	231-232 ⁸
13	C ₆ H ₅ CH=CH	3m	1	88	214-215	216 ¹⁴
14	4-Cl C ₆ H ₄	3c	2	91-93 ^d	289-290	289-291 ⁸

^a All reactions were run with aromatic aldehydes (1mmol) and 1,3-cyclohexanedione (2mmol) in [Hmim]HSO₄ (2ml) at 80°C. ^b Isolated yields. ^c Melting points were uncorrected. ^d yields of second to 6th run recycling of [Hmim]HSO₄ were 92%, 91%, 92%, 93%, 92% ordinally.

Conclusion

In conclusion, we have demonstrated that the condensation of 1, 3-cyclohexanedione with aromatic aldehydes could be effectively catalyzed by acid ionic liquid [Hmim]HSO₄, which play a dual role as solvent and catalyst in this reaction. The present method has many obvious advantages compared to previous methods, including no need for the use of any added catalyst, being environmentally more benign, ease of product isolation, simplicity of methodology, high yield, and potential for recycling of ionic liquid and generality.

Experimental

Melting points were determined on digital melting point apparatus and were not corrected. Infrared spectra were recorded on an AVATAR-360 Infrared Spectrophotometer. ¹H NMR spectra were recorded on a BRUKER-400MHz spectrometer using CDCl₃ as the solvent with tetramethylsilane (TMS) as an internal standard. The ionic liquids [HSO₃(CH₂)₃mim]HSO₄, [HSO₃(CH₂)₃mim]H₂PO₄, [HSO₃(CH₂)₃mim]CF₃SO₃ were synthesized as lit.,¹⁵ [Hmim]HSO₄, [Hmim]H₂PO₄ was synthesized as lit.,¹⁶ [Hmim]CF₃COO was synthesized as lit.,¹⁷ [Bmim]HSO₄ was synthesized as lit.,¹⁸ [Bmim]BF₄ and EAN was synthesized as lit.¹⁹ and lit.²⁰ respectively.

General procedure for the preparation of 3a–3m

1, 3-cyclohexanedione 1 (2 mmol), Aromatic aldehyde 2 (1 mmol) were added in ionic liquid (2 mL). The reaction mixture was stirred at 80 °C for an appropriate time, reaction was monitored by thin layer chromatography (TLC). Upon completion of the reaction, after filtering the solid directly from the reaction mixture and washing with water and cold ethanol successively, gave the desired products 3 in high yields with essential purity. After isolation of the product, the remainder of the ionic liquids was dried for 4 h under vacuum at 70 °C. The next run was performed under identical reaction conditions.

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