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

Hui Kang, Yi Hu*, He Huang and Ping Wei
College of Life Science and Pharmaceutical Engineering, Nanjing University of Technology, Nanjing, 210009, P. R. China
e-mail: huyi@njut.edu.cn

Abstract : An efficient and convenient approach to the synthesis of 9-aryl-2, 3, 4, 5, 6, 7-hexahydro-2H-Xanthene-1, 8-dionc by condensation of 1, 3-cyclohexanedione with aromatic aldehydes catalyzed by acid ionic liquid 1- methyllimidazolium hydrogen sulphate ([Hmim]HSO_4) 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] TiO_2/SO_4^{2-},[4] acidic resin amberlyst-15,[5] polyaniline-p-tolulenesulfonate salt,[6] phase transfer catalysts,[7] or facilitated by MW irradiation[8] 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]BF_4) could be used as a green reaction medium, using $FeCl_3{\cdot}6H_2O$,[10] $InCl_3{\cdot}4H_2O$[11] or $NaHSO_4$[12] 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]HSO_4 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]BF_4 and ethylammonium nitrate (EAN). Obviously, [Hmim]HSO_4 showed the best result, which play a dual role as solvent and promoter in this reaction. So we selected the [Hmim]HSO_4 as reaction medium in the following reactions.

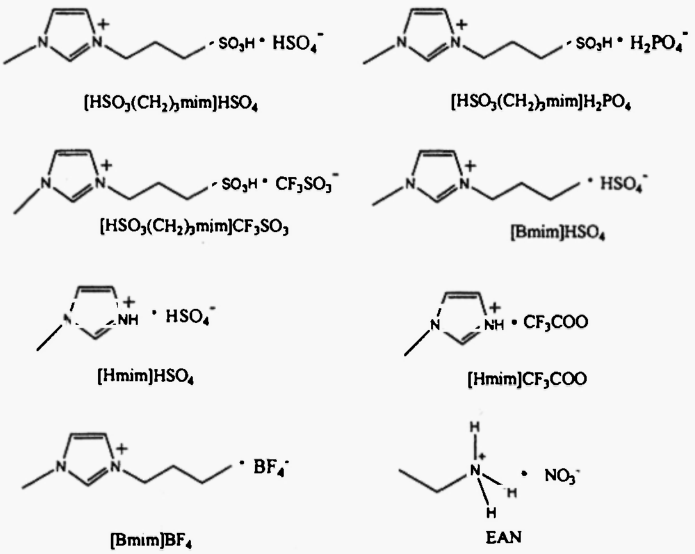
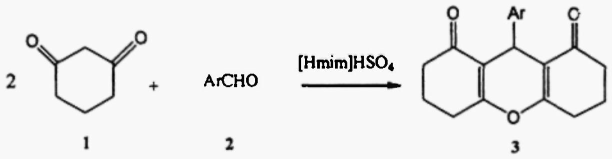


Fig. 1 Structure of ionic liquids

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

Entry[a]	**Ionic liquids (IL)**	**Yield (%)**[b]
1	$[HSO_3(CH_2)_3mim]HSO_4$	84
2	$[HSO_3(CH_2)_3mim]H_2PO_4$	88
3	$[HSO_3(CH_2)_3mim]CF_3SO_3$	71
4	$[Bmim]HSO_4$	67
5	$[Hmim]CF_3COO$	86
6	$[Hmim]HSO_4$	93
7	EAN	61
8	$[Bmim]BF_4$	13

[a] All reactions were run with 4-methoxylbenzaldehyde (1mmol) and 1,3-cyclohexanedione (2mmol) in ionic liquid (2ml) at 80℃ 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 $[Hmim]HSO_4$ 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 adehyde, 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]HSO_4 [a]

Entry	Ar	Product	Time/ h	Yield /% [b]	Mp/□[c]	Lit. Mp/□
1	C_6H_5	3a	2	82	267-268	270-271[8]
2	4-CH_3O C_6H_4	3b	4	93	206-207	204-206[12]
3	4-Cl C_6H_4	3c	2	92	289-290	289-291[8]
4	4-Br C_6H_4	3d	2	93	284-285	285-286[8]
5	4-NO_2 C_6H_4	3e	2	93	265-267	265-266[8]
6	3-OH C6H4	3f	2	89	255-257	257[14]
7	3-NO_2 C_6H_4	3g	2	78	282-284	286-288[8]
8	2-OH C6H4	3h	3	88	230-231	233[14]
9	2-Cl C_6H_4	3i	3	85	250-251	250-251[8]
10	3-OCH_3-4-OH C_6H_3	3j	4	87	238-239	242-243[12]
11	3,4-Cl,Cl C_6H_3	3k	3	76	232-234	231-232[8]
12	2,4-Cl,Cl C_6H_3	3l	3	74	230-231	231-232[8]
13	$C_6H_5CH{=}CH$	3m	1	88	214-215	216[14]
14	4-Cl C_6H_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]HSO_4 (2ml) at 80□. [b] Isolated yields. [c] Melting points were uncorrected. [d] yields of second to 6th run recycling of [Hmim]HSO_4 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]HSO_4, 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. ^{1}HNMR spectra were recorded on a BRUKER-400MHz spectrometer using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard. The ionic liquids [$HSO_3(CH_2)_3$mim]HSO_4 , [$HSO_3(CH_2)_3$mim]H_2PO_4, [$HSO_3(CH_2)_3$mim]CF_3SO_3 were synthesized as lit.,[15] [Hmim]HSO_4, [Hmim]H_2PO_4 was synthesized as lit.,[16] [Hmim]CF_3COO was synthesized as lit.,[17] [Bmim]HSO_4 was synthesized as lit.,[18] [Bmim]BF_4 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□ 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 4h under vacuum at 70□. The next run was performed under identical reaction conditions.

References

(1) J. Kuthan, P. Sebek and S. Bohm, Advances in Heterocyclic Chemistry, Vol. 62, Academic Press Inc., New York, 1995.
(2) M. Suárez, Y. Verdecia, E. Ochoa, E. Salfán, L. Morán, N. Martin, R.Martine, M. Uinteiro, C. Seoane, J. L. Soto, H. Novoa, N. Blaton, O. M. Peeters and C. D. Ranter, Eur. J. Org. Chem. (11), 2079 (2000).
(3) J. R. Dimmock, S. K. Raghavan and G. E. Bigam, Eur. J. Med. Chem. 23, 111, (1988).
(4) T. S. Jin, J. S. Zhang, A. Q. Wang and T. S. Li, Synth. Commun. 35, 2339, (2005).
(5) B. Das, P. Thirupathi, I. Mahender, V. S. Reddy and Y. K. Rao, J. Mol. Cata. A: Chem. 247, 233 (2006).
(6) A. John, P. J. P.Yadav and S. Palaniappan, J. Mol. Cata. A: Chem. 248, 121, (2006).
(7) (a) T. S. Jin, J. S. Zhang, J. C. Xiao, A. Q. Wang and T. S. Li, Synlett, 866, (2004).
(b) T. S. Jin, J. S. Zhang, A. Q. Wang and F. S. Zhang, Chin. J. Org. Chem. 25, 335 (2005).

(8) G. P. Hua, T. J. Li, S. L. Zhu and X. J. Zhang, Chin. J. Org. Chem. 25, 716, (2005).

(9) T. S. Jin, J. S. Zhang, A. Q. Wang and T. S. Li, Ultrason. Sonochem. 13, 220, (2006).

(10) X. S. Fan, Y. Z. Li, X. Y. Zhang, X. Y. Hu and J. J. Wang, Chin. J. Org. Chem. 25, 1482 (2005).

(11) X. Y.Hu, X. S. Fan, X. Y. Zhang and J. J. Wang, Chin. Chem.Lett. 16, 293, (2005).

(12) J. J. Ma, J. C. Li, R. X. Tang, X. Zhou, Q. H. Wu, C. Wang, M. M. Zhang and Q. Li, Chin. J. Org. Chem. 27, 640 (2007).

(13) (a) Y. Hu, P. Wei, H. Huang, Z. G. Le and Z. C. Chen, Synth. Commun. 35, 2955 (2005).

(b) Y. Hu, J. Chen, Z. G.Le and Q. G. Zheng, Synth. Commun. 35, 739 (2005).

(14) F. E. King and D. G. Felton, J. Chem. Soc. 1371 (1948,)

(15) D. M. Li, F. Shi, J. J. Peng, S. Guo and Y. Q. Deng, J. Org. Chem. 69, 2004, (3582).

(16) G. Y. Zhao, T. Jiang, H. X. Gao, B. X. Han, J. Huang and D. H. Sun, Green. Chem. 6, 75 (2004).

(17) G. Q. Lai, F. M. Ma and Z. Q. Hu, Chin. Chem.Lett. 18, 601 (2007).

(18) V. Singh, S. Kaur, V. Sapehiyia, J. Singh and G. L. Kad, Catal. commun. 6,57, (2005).

(19) G. S. Owens and M. M. Abu-Omer, J. Mol. Catal. A: Chem. 187, 215 (2002).

(20) F. Pacholec, H. T. Butler and C. F. Poole, Anal. Chem

Received on January 21,2008