Facile synthesis of 3-arylidene-1,3-dihydroindol-2-ones catalysed by a Brønsted acidic ionic liquid

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A series of 3-arylidene-1,3-dihydroindol-2-one derivatives were conveniently synthesised by the condensation of aromatic aldehydes with 1,3-dihydroindol-2-one using a Brønsted acidic ionic liquid as a dual solvent-catalyst. This method has the advantages of short reaction times, simple work-up, high yields with high purity, being environmentally benign and the ionic liquid can be reused.

Keywords: ionic liquids, 1,3-dihydroindol-2-one, aromatic aldehydes, condensation

3-Arylidene-1,3-dihydroindol-2-one derivatives constitute an important class of chemically, biologically and pharmaceutically significant compounds.[1-3] Generally, these derivatives can be obtained by the Knoevenagel condensation of 1,3-dihydroindol-2-one with aromatic aldehydes catalysed by an organic base such as pyridine[2,4-9] and piperazine [9,10] in a volatile organic solvent. Long reaction times are needed to complete these reactions and sometimes only moderate yields are obtained. Recently, various efficient methods have been developed such as facilitation by MW irradiation,[8,11,12] phase transfer catalysts,[13] or under strong basic and solvent-free conditions by grinding.[3] However, some of these methods are limited by using an environmentally unfriendly solvent, using an expensive catalyst, being difficult to carry out on a large scale or having tedious workup. Considering the importance of 3-arylidene-1,3-dihydroindol-2-one derivatives, we think it is still important to develop more facile and efficient methods with environmentally benign technologies to prepare these compounds.

In recent years, the interest in room temperature ionic liquids has increased as green reaction media for synthetic organic chemistry.[14,15] In continuation of our interest in using ionic liquids as eco-friendly media and catalysts for condensation reactions,[16,17] we report here that 1,3-dihydroindol-2-one reacts with aromatic aldehydes smoothly in the functional Brønsted acid ionic liquid (1-(3-sulfonic acid)propyl-3-methylimidazolium hydrogen sulfate ($[(CH_2)_3SO_3Hmim]HSO_4$).

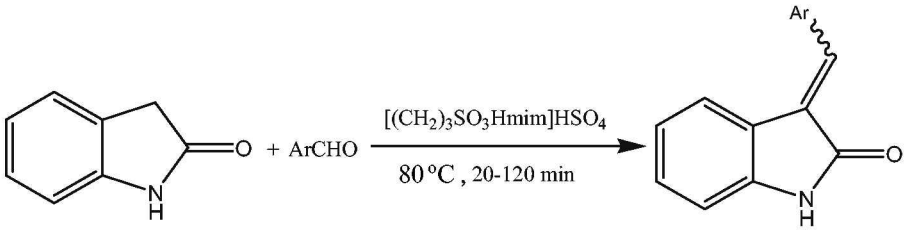
The results are summarised in Table 1. All the products were characterised by ^{1}H NMR, IR and the data were consistent with the literature data. As can be seen from the results in Table 1 that this procedure was found to be general and applicable to aromatic aldehydes bearing various substituents such as chloro, bromo, nitro, methoxy, hydroxyl, *etc.* Note that aromatic aldehydes bearing electron-donating groups reacted more easily compared with those containing electron-withdrawing groups, which is consistent with our previous reports,[16,17] and in contrast with literature reports.[3,11-13] Perhaps it is a consequence of the pre-equilibrium between the aldehyde and (reactive) protonated aldehyde sitting more over to the right-hand side in the case of the aromatic aldehyde substituted by electron-donating groups. The reaction of the hindered aromatic aldehyde 2,6-dichlorobenzaldehyde (Entry 11) and the aromatic α,β-unsaturated aldehyde, 2-furancarboxaldehyde (Entry 15) and cinnamaldehyde (Entry 16) with 1,3-dihydroindol-2-one also could be completed efficiently with high yields obtained. Moreover, the functional ionic liquid $[(CH_2)_3SO_3Hmim]HSO_4$ could typically be recovered and reused with no appreciable decrease in yields and reaction rates (Entries 2 and 3). Disappointedly, simple as this reaction is, we could not obtain satisfactory results when it was applied to aliphatic aldehydes and ketones under the same reaction conditions.

In order to compare with the reported procedures, some representative literature data are summarised in Table 2.

In conclusion, we have demonstrated that 3-arylidene-1,3-dihydroindol-2-one derivatives can be conveniently synthesised by the condensation of 1,3-dihydroindol-2-one with aromatic aldehydes in the functional Brønsted acid ionic liquid $[(CH_2)_3SO_3Hmim]HSO_4$, which plays a dual role as the solvent and the catalyst. The present method has many advantages compared to the previous methods, including no need for the use of any additional added catalyst, being more environmentally acceptable, ease of product isolation, experimental simplicity, high yield and the potential for recycling of the ionic liquid.

Experimental

Melting points were determined on digital melting point apparatus and were not corrected. Infrared spectra were recorded on an AVATAR-360 IR spectrophotometer. ^{1}H NMR spectra were recorded on a BRUKER-300 MHz spectrometer using DMSO-d_6 as the solvent with tetramethylsilane (TMS) as an internal standard. Elemental analysis was performed on an Elementar Vario MICRO analyser. The ionic liquid $[(CH_2)_3SO_3Hmim]HSO_4$ was synthesised as described.[18] All other materials are commercially available and were used without further purification.



1 2 3

Scheme 1

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Table 1 Condensation of 1,3-dihydroindol-2-one with aromatic aldehydes in $[(CH_2)_3SO_3Hmim]HSO_4$

Entry[a]	Ar	Time/min	Product[b]	Yield[c]/%	Mp[d]/°C	Lit.m.p./°C
1	p-$MeOC_6H_4$	20	**3a**	97	142–144	159–160[3]
2	p-$MeOC_6H_4$	20	**3a**	95[d]		
3	p-$MeOC_6H_4$	20	**3a**	96[e]		
4	3-OCH_3-4-OHC_6H_3	40	**3b**	96	226–227	227–228[8]
5	3,4-$OCH_2OC_6H_3$	40	**3c**	94	210–211	210[11]
6	o-OHC_6H_4	60	**3d**	91	198–199	195–196[6]
7	C_6H_5	60	**3e**	93	175–176	175–176[3]
8	p-ClC_6H_4	60	**3f**	94	187–188	188–190[3]
9	o-ClC_6H_4	60	**3g**	86	177–179	177–178[3]
10	3,4-Cl,ClC_6H_3	100	**3h**	89	195–197	208–210[13]
11	2,6- Cl,ClC_6H_3	120	**3i**	88	188–189	164[11]
12	p-BrC_6H_4	60	**3j**	92	191–192	195–196[19]
13	m-$NO_2C_6H_4$	60	**3k**	95	209–210	217–218[13]
14	o-$NO_2C_6H_4$	60	**3l**	93	234–235	236–238[13]
15	2-furaryl	90	**3m**	91	181–182	183[11]
16	C_6H_5CH=CH	60	**3n**	95	208–210	206[11]

[a]All reactions were run with 1,3-dihydroindol-2-one (1 mmol) and aromatic aldehyde (1 mmol) in $[(CH_2)_3SO_3Hmim]HSO_4$ (2 ml) at 80 °C. [b]The details of the geometric isomerism, (*E*/*Z* ratio) of the product is under investigation. [c]Isolated yield. [d]Melting points were uncorrected. [e-f]Second and third recycling of $[(CH_2)_3SO_3Hmim]HSO_4$.

Table 2 Condensation of 1,3-dihydroindol-2-one with aromatic aldehydes under different reaction conditions

Product	Yield/% This work	Yield/% Literature work	Literature work
3e	93	72[13]	Catalysed by triethylbenzylammonium chloride at r.t. for 24 h in water
		65[9]	KF/Al_2O_3, microwave irradition, 60 W, 5 min
		94[12]	DMF, microwave irradition, 600 W, 3 min
3g	90	90[3]	Catalysed by KOH, by grinding at r.t. for 10 min
		81[11]	KF/Al_2O_3, under focused microwaves in resonance cavity TE_{01} at 2450 MHz, 2.5 min
		81[12]	DMF, microwave irradition, 600 W, 2.5 min.
		56[6]	Catalysed by piperidine at 90 °C for 3–5 h in ethanol
3i	88	85[6]	Catalysed by piperidine at 90 °C for 3–5 h in ethanol
		69[12]	DMF, microwave irradition, 600 W, 3.5 min.
		69[11]	KF/Al_2O_3, under focused microwaves in resonance cavity TE_{01} at 2450 MHz, 3.5 min

General procedure for the preparation of **3a–3n**

1,3-Dihydroindol-2-one **1** (1 mmol), aromatic aldehyde **2** (1 mmol) were added to the ionic liquid $[(CH_2)_3SO_3Hmim]HSO_4$ (2 ml). The reaction mixture was stirred at 80 °C, and the reaction was monitored by TLC. Upon completion of the reaction, the solid was filtered directly from the reaction mixture and washed with water to give the desired product **3** in high yield and purity. After isolation of the product, the remaining ionic liquid was dried for 4 h under vacuum at 70 °C. The next run was performed under identical reaction conditions.

Spectroscopic data for **3a, 3h, 3i, 3j and 3k**

3a: IR (KBr): 3165, 3074, 1702, 1665, 1601, 1510, 1462, 1421 cm^{-1}. ^1H NMR (DMSO-d_6):δ = 3.90 (s, 3H), 6.88-6.98 (m, 2H), 7.00 (d, J = 9.2 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 7.68 (d, J = 9.2 Hz, 2H), 7.77 (d, J = 7.2 Hz, 1H), 7.81 (s, 1H), 8.87 (s, 1H); Found: C, 76.32; H, 5.27; N, 5.58. Calcd for $C_{16}H_{13}NO_2$: C, 76.48,; H, 5.21; N, 5.57%.

3h: IR (KBr): 3151, 3073, 1717, 1611, 1461 cm^{-1}. ^1H NMR (DMSO-d_6):δ = 6.84–6.89 (m, 2H), 7.56 (s, 1H),7.68–7.80 (m, 4H), 7.95 (d, J = 6.0 Hz, 1H), 8.81(s, 1H). Found: C, 62.01; H, 3.17; N, 5.05. Calcd for $C_{15}H_9Cl_2NO$: C, 62.09; H, 3.13; N, 4.83%.

3i: IR (KBr): 3154, 3083, 3026, 1708, 1646, 1615, 1463, 1428 cm^{-1}. ^1H NMR (DMSO-d_6):δ = 6. 45 (d, J = 7. 5 Hz, 1H), 6.71–6.85 (m, 2H), 7.18–7. 23(m, 1H), 7.48–7.53 (m, 2H), 7.64 (d, J = 9.0 Hz, 1H), 8.3 (br s, 1H),10.72 (s, 1H). Found: C, 62.03; H, 3.15; N, 4.91. Calcd for $C_{15}H_9Cl_2NO$: C, 62.09; H, 3.13; N, 4.83%.

3j: IR (KBr): 3174, 3071,3025, 1704, 1616, 1583, 1484, 1461 cm^{-1}. ^1H NMR (DMSO-d_6):δ = 6.83–6.89 (m, 2H), 7.22–7.27 (m, 1H), 7.47–7.69 (m, 5H), 7.71 (s, 1H), 10.63 (s, 1H). Found: C, 60.12; H, 3.23; N, 4.69. Calcd for $C_{15}H_{10}BrNO$: C, 60.02; H, 3.36; N, 4.67%.

3k: IR (KBr): 3162, 3092, 1714, 1615,1529, 1469 cm^{-1}. ^1H NMR (DMSO-d_6):δ = 6.83–6.91 (m, 2H), 7.23–7.29 (m, 1H),7.68–7.84 (m, 2H), 7.97 (s, 1H), 8.13 (d, J = 7.8 Hz, 1H), 8.26–8.32 (m, 1H), 8.52 (s, 1H); 9.39 (s, 1H). Found: C, 67.79; H, 3.71; N, 10.62. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.79; N, 10.52%.

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References

1 N. Finch and W.I. Taylor, *J. Am. Chem. Soc.*, 1962, **84**, 1318.
2 L. Sun, N. Tran, F. Tang, H. App, P. Hirth, G. McMahon and C. Tang, *J. Med. Chem.*, 1988, **41**, 2588.
3 T.T. Xu, S.Y. Wang and S.J. Ji, *Chin. J. Org. Chem.*, 2006, **26**, 1414.
4 I.W. Elliott and P. Rivers, *J. Org. Chem.*, 1964, **29**, 2438.
5 S.E. Boiadjiev and D.A. Lightner, *Monatsh. Chem.*, 2003, **134**, 489.
6 S. Olgen, E. Akaho and D. Nebioglu, *Il Farmaco,* 2005, **60**, 4979.
7 S. Olgen, S. Gotz and J. Jose, *Biol. Pharm Bull.*, 2007, **30**, 715.
8 Z.L. Min, F.C. Jiang and Q. Zhang, *Chin. J. Med. Chem.*, 2005, **15**, 129.
9 K. Ding, G.P. Wang, J.R. Deschamps, D.A. Parrish and S.M. Wang, *Tetrahedron Lett.*, 2005, **46**, 5949.
10 A. Andreani, M. Rambaldi, A. Locatelli, R. Bossa, I. Galatulas and M. Ninci, *Eur. J. Med. Chem.*, 1990, **25**, 187.
11 D. Villemin and B. Martin, *Synth. Commun.*, 1998, **28**, 3201.
12 M.S. Wu and X.Z. Zhang, Chin. *J. Org. Chem.*, 2002, **22**, 149.
13 X.S.Wang, Z.S. Zeng, Y.L. Li, D.Q. Shi, S.J. Tu, X.Y. Wei and Z.M. Zong, *Chin. J. Org. Chem.*, 2005, **25**, 1598.
14 P. Wasserscheid and T. Welton, *Ionic liquids in synthesis.* VCH Wiley, Weinheim, Germany, 2003.
15 V.I. Parvulescu and C. Hardacre, *Chem. Rev.*, 2007, **107**, 2615.
16 Y. Hu, P. Wei, H. Huang, Z.G. Le and Z.C. Chen, *Synth. Commun.*, 2005, **35**, 2955.
17 Y. Hu, P. Wei, H. Zhou, P.K. Ouyang and Z.C. Chen, *Chin. Chem. Lett.*, 2006, **17**, 299.
18 D.M. Li, F. Shi, J.J. Peng, S. Guo and Y.Q. Deng, *J. Org. Chem.*, 2004, **69**, 3582.
19 C.C. Andreina, G.I. Anna, P.R. Pier and T. Gianfranco, *J. Chem. Soc., Perkin Trans 2,* 1984, 615.