FACILE SYNTHESIS OF 3-ARYLIDENE-1,3-DIHYDROINDOL-2-ONES CATALYZED BY BRØNSTED ACIDIC IONIC LIQUIDS

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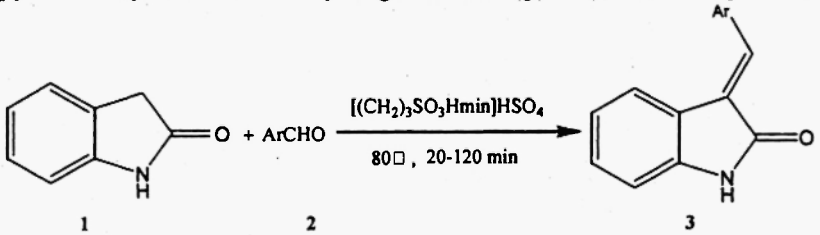
Abstract : A series of 3-arylidene-1,3-dihydroindol-2-one derivatives were conveniently synthesized by the condensation of aromatic aldehydes with 1,3-dihydroindol-2-one using brØnsted acidic ionic liquids as dual solvent-catalyst. This method has the advantages of short reaction times, simple work-up, high yields with high purity, environmentally benign and the reusability of ionic liquids.

Introduction

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 catalyzed by organic base such as pyridine[2] [4-9] and piperazine [9-10] in the volatile organic solvent, while long reaction times were needed to completed these reactions and sometimes only moderate yields obtained. Recently, various efficient methods have been developed such as facilitated 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 due to using environmental unamiable solvent, expensive catalyst, difficult to prepare in large scale, tedious workup, unsatisfactory yields, etc. Considering the importance of 3-arylidene-1,3-dihydroindol-2-one derivatives, we think it is still significant 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 is increasing as green reaction media for synthetic organic chemistry.[14-15] In continuation of our interest in using ionic liquids as eco-friendly medium and catalyst for the condensation reactions,[16-17] we report herein 1,3-dihydroindol-2-one could be reacted with aromatic aldehydes smoothly in the functional brØnsted acid ionic liquid (1-(3-sulfonic acid)propyl-3-methylimidazolium hydrogen sulfate ([$(CH_2)_3SO_3H$min]HSO_4).



Scheme 1

Results and Discussion

The results are summarized in Table 1. All the products were characterized by ^1H NMR, IR and that were consistent with the literature data. As can be seen from the table 1 that this procedure was found to be general and applicable to the aromatic

aldehydes bearing various substituents such as choloro, bromo, nitro, methoxyl, hydroxyl, etc. It is noteworthy that aromatic aldehydes bearing electron-donating groups reacted more easily compared with those containing electron-withdrawing groups the same as our previous report described,[16-17] and as is different from the previous literatures.[3,11-13] Besides, the reaction of the hindered aldehyde 2,6-dichlorobenzaldehyde (Entry 11) and the aromatic α,β-unsaturated aldehyde, 2-furancarboxaldehyde (Entry 15) and Cinnamic aldehyde (Entry 16) with 1,3-dihydroindol-2-one also could be completed efficiently with high yields obtained. Moreover, the functional ionic liquid $[(CH_2)_3SO_3Hmin]HSO_4$ could be typically recovered and reused with no appreciable decrease in yields and reaction rates (Entry 2-3).

Table 1 Condensation of 1,3-dihydroindol-2-one with aromatic aldehydes in ionic liquids

Entry[a]	Ar	Time(min)	Product	Yield[b](%)	Mp[c](□)	Lit.mp(□)
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-OH C_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,Cl C_6H_3	100	3h	89	195-197	208-210[13]
11	2,6- Cl,Cl C_6H_3	120	3i	88	188-189	164[11]
12	4-Br C_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-furfuraly	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 $[(CH_2)_3SO_3Hmin]HSO_4$ (2ml) at 80□. [b] Isolated yield. [c] Melting points were uncorrected. [d-e] Second and third recycling of $[(CH_2)_3SO_3Hmin]HSO_4$.

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

Table 2 Condensation of 1,3-Dihydroindol-2-one with Aromatic Aldehydes under Different Reaction Conditions

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

Conclusion

In conclusion, we have demonstrated that 3-arylidene-1,3-dihydroindol-2-one derivatives could be conveniently synthesized by the condensation of 1,3-dihydroindol-2-one with aromatic aldehydes in functional brØnsted acid ionic liquid $[(CH_2)_3SO_3Hmin]HSO_4$, which play a dual role as solvent and catalyst in this reaction. The present method has many obvious advantages compared to the 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, potential for recycling of ionic liquid and the 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-300MHz spectrometer using DMSO-d_6 as the solvent with tetramethylsilane (TMS) as an internal standard. Elemental analysis was performed on an Elementar Vario MICRO analyzer. The ionic liquids $[(CH_2)_3SO_3Hmin]HSO_4$ was synthesized as lit.[18] All other materials are commercially available and were used without further purification.

General procedure for the preparation of 3a~3n

1,3-dihydroindol-2-one 1(1 mmol), aromatic aldehyde 2(1 mmol) were added in ionic liquid $[(CH_2)_3SO_3Hmin]HSO_4$ (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, 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.

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); Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48,; H, 5.21; N, 5.57. Found: C, 76.32; H, 5.27; N, 5.58.

3h: IR (KBr): 3151, 3073, 1717, 1611, 1461cm^{-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). Anal. Calcd for $C_{15}H_9Cl_2NO$: C, 62.09; H, 3.13; N, 4.83. Found: C, 62.01; H, 3.17; N, 5.05.

3i: IR (KBr): 3154, 3083, 3026, 1708, 1646, 1615, 1463, 1428 cm^{-1}. ^1H NMR (DMSO-d_6):δ= 6. 44 6.47(d , J = 7. 5 Hz, 1H) , 6.71~6.85 (, 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). Anal. Calcd for $C_{15}H_9Cl_2NO$: C, 62.09; H, 3.13; N, 4.83. Found: C, 62.03; H, 3.15; N, 4.91.

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). Anal. Calcd for $C_{15}H_{10}BrNO$: C, 60.02; H, 3.36; N, 4.67. Found: C, 60.12; H, 3.23; N, 4.69.

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). Anal. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.79; N, 10.52. Found: C, 67.79; H, 3.71; N, 10.62.

Acknowledgments

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