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[Hmim][HSO_4]: An Efficient and Reusable Catalyst for the Synthesis of Spiro[dibenzo[*a,i*]-xanthene-14,3'-indoline]-2',8,13-triones and Spironaphthopyran[2,3-*d*]pyrimidine-5,3'-indolines

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Indole moiety is probably the most well-known heterocycle and a common and important feature of a variety of natural products and medicinal agents.[1] Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhances biological activity.[2,3] The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.[4,5] Therefore, a number of methods have been reported for the preparation of spirooxindole fused heterocycles.[6-10] The quinone moiety is involved in a wide variety of biochemical processes including electron transport and oxidative phosphorylation.[11] Various biological properties including enzyme inhibition, antibacterial, antifungal, and anticancer activities have been reported for quinones.[12,13] The antitumor activity of the quinone moiety has been studied thoroughly, and it is known that they act as topoisomerase inhibitors *via* DNA-intercalation.[14] Quinone-annulated heterocycles are found in nature, and most of them exhibit interesting biological activities. The chemistry of quinone-annulated heterocycles is dependent largely on the substituent being either on the quinone or on adjacent rings.[15] These activities, combined with diverse chemical behavior make quinones attractive targets in organic synthesis.

The removal of volatile organic solvents in organic reactions is the most important goal in green chemistry. One of the most efficient protocols to reach this aim is replacement of the volatile solvents with ionic liquids possessing low volatility, high thermal stability, non-flammability, recyclability and unique catalytic activity. During recent years, ionic liquids have attracted interest as environmentally benign reagents due to their favorable properties and a variety of catalytic reactions have been successful using ionic liquids.[16-19]

Considering the above reports, and as part of our program aimed at developing new selective and environmentally friendly methodologies for the preparation of heterocyclic compounds,[20,21] we undertook the synthesis of spiro[dibenzo[*a,i*]- xanthene-14,3'-indoline]-2',8,13-triones through a cyclo-condensation reaction between β-naphthol, isatins, and 2-hydroxynaphthalene-1,4-dione in the presence of a catalytic amount of [Hmim][HSO_4] (Figure 1) as an efficient and reusable catalyst. During our study, we also observed

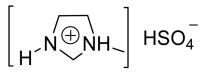
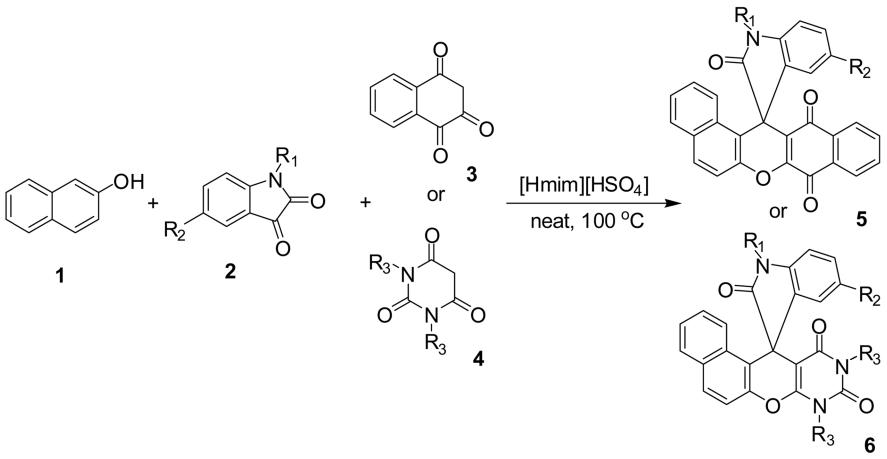


Figure 1. The structure of [Hmim][HSO_4].



Scheme 1

formation of spironaphthopyrano[2,3-*d*] pyrimidine-5,3'-indoline in excellent yields by one-pot condensation of β-naphthol with isatins and barbituric acids in the presence of [Hmim][HSO_4] (Scheme 1).

In the preliminary stage of investigation we focused on systematic evaluation of different catalysts for the model reaction of β-naphthol, isatin, and 2-hydroxynaphthalene-1,4-dione at 100 °C under solvent-free conditions. A wide variety of catalysts including H_2SO_4, HCl, *p*-TsOH, NH_2SO_3H, $FeCl_3$, $ZnCl_2$, [Bmim]Br, [Hmim][HSO_4], [Emim][HSO_4] and [Bmim][HSO_4], were employed to improve the yield for the specific synthesis of spiro[dibenzo[*a,i*]-xanthene-14,3'-indoline]-2',8,13-triones. The results are presented in Table 1. the reaction proceeded efficiently in acidic ionic liquid [Hmim][HSO_4], [Emim][HSO_4] and [Bmim][HSO_4] (entries 8-10). The catalytic performance of [Hmim][HSO_4], [Emim][HSO_4] and [Bmim][HSO_4] was found to be same indicating that there was little impact of the cation on the catalytic activity. Attempts to perform the reaction in [Bmim]Br led only low yields of the products even at prolonged reaction time. These results suggest that the catalytic activity of the ionic liquids on the condensation reaction was dependent on the Brønsted acidity of the counteranion. The catalytic performance of the ionic liquids with hydrogen sulphate counteranion was found to be better than that of the other employed ionic liquids under the same reaction conditions. Probably, this is due to the high Brønsted acidity of hydrogen sulphate counteranion. So [Hmim][HSO_4] was chosen for all further study in this work.

In the next step, the scope and efciency of the catalyst were explored under the optimized reaction conditions for the condensation of β-naphthol with a broad range of structurally diverse isatins and 2-hydroxynaphthalene-1,4-dione to furnish the corresponding products. The results are displayed in Table 2. As it can be seen the spiro[dibenzo[*a,i*]-xanthene-14,3'-indoline]-2',8,13-trione derivatives were obtained in high yields and short reaction times. The inuence of electron-withdrawing and electron-donating substituents

Table 1. Effect of catalyst on the formation of spiro[dibenzo[*a,i*]-xanthene-14,3'- indoline]-2',8,13-trione[a]

Entry	Catalyst	Time/h	Yield/%[b]
1	H_2SO_4	2	52
2	HCl	2	41
3	*p*-TsOH	1	80
4	NH_2SO_3H	1.5	69
5	$FeCl_3$	2	49
6	$ZnCl_2$	2	51
7	[Bmim]Br	3	56
8	[Hmim][HSO_4]	1.5	91
9	[Emim][HSO_4]	1.5	88
10	[Bmim][HSO_4]	1.5	87
11	-	4	0

[a]Reaction conditions: β-naphthol (1 mmol); isatin (1 mmol); 2-hydroxynaphthalene-1,4-dione (1 mmol); catalyst (0.05 mmol); 100 °C; neat. [b]Isolated yield.

Table 2. Preparation of spiro[dibenzo[*a,i*]-xanthene-14,3'-indoline]-2',8,13-triones[a]

Entry	R^1	R^2	Time/h	Product	Yield/%[b]
1	H	H	1.5	**5a**	91 (89, 85, 82)[c]
2	H	Cl	1.5	**5b**	90
3	H	Me	1	**5c**	93
4	H	F	1.5	**5d**	89
5	H	Br	1.5	**5e**	88
6	Me	H	2	**5f**	84

[a]Reaction conditions: β-naphthol (1 mmol); isatins (1 mmol); 2-hydroxynaphthalene-1,4-dione (1 mmol); catalyst (0.05 mmol); neat; 100 °C. [b]Isolated yield. [c]The catalyst was reused for three runs

of isatins upon the reaction yields was investigated. The results showed that both electron-withdrawing and electron-donating substituents had no signicant effect on the reaction yields. Compounds **5** are stable solids whose structures were established by IR, ^{1}H NMR spectroscopy, MS and elemental analysis. The experimental procedure is remarkably simple because after the completion of the reaction, water was added to the reaction mixture and the insoluble crude products were isolated by simple ltration and recrystallized to obtain pure products. In order to resumption of catalyst, water was evaporated in reduced pressure and recovered catalyst was washed by diethyl ether two times and reused for another reaction. Any loose of rates or yields was observed by use of recovered [Hmim][HSO_4] for three cycle of reactions (Table 2, entry 1).

The proposed mechanism for the synthesis of spirooxindole derivative **5** is described in Scheme 2. In this process, the β-naphthol **1** rst condenses with isatins **2** to afford intermediate **7** in the presence of [Hmim][HSO_4]. Then, subsequent addition of 2-hydroxynaphthalene-1,4-dione to the intermediate **7**, followed by cyclization afforded the **5** and water.

After the successful synthesis of spiro[dibenzo[*a,i*]-xanthene-14,3'-indoline]-2',8,13-triones, this catalytic system was used for the synthesis of spironaphthopyrano[2,3-*d*]pyrimidine-5,3'-indolines. For this purpose, β-naphthol and isatins were condensed with barbituric acids **4** under optimized reaction conditions to afford the corresponding products. The results of the reactions are summarized in Table 3.

Table 3. Preparation of spironaphthopyrano[2,3-*d*]pyrimidine-5,3'-indolines[a]

Entry	R^1	R^2	R^3	Time/h	Product	Yield/%[b]	Ref.
1	H	H	H	1.5	**6a**	88	22
2	H	H	Me	1	**6b**	86	22
3	H	Br	H	1.5	**6c**	85	22
4	H	Br	Me	2	**6d**	82	22
5	Me	H	H	1	**6e**	90	22
6	Me	H	Me	1.5	**6f**	87	22

[a]Reaction conditions: β-naphthol (1 mmol); isatins (1 mmol); barbituric acids (1 mmol); catalyst (0.05 mmol); neat; 100 °C. [b]Isolated yield

In conclusion, an extremely efficient method has been developed for the synthesis of novel spiro[dibenzo[*a,i*]-xanthene-14,3'-indoline]-2',8,13-triones and spironaphthopyrano[2,3-*d*]pyrimidine-5,3'-indolines *via* a one-pot three-component condensation reaction using [Hmim][HSO_4] as an efficient and reusable catalyst. This method is bestowed with several unique merits, such as high conversions, simplicity in operation, cost efciency, use of solvent-free and mild conditions, simple workup, high yields and usage in synthesis of complex molecules.

Experimental Section

General Procedure for the Preparation of 5 and 6. A mixture of β-naphthol (1 mmol), isatins (1 mmol), 2-hydroxynaphthalene-1,4-dione or barbituric acids (1 mmol), and [Hmim][HSO_4] (0.05 mmol) was heated at 100 °C for an appropriate time (TLC). After completion, the reaction mixture was washed with water (10 mL) and residue recrystallized from EtOH to afford the pure product **5** and **6**. Aqueous washings were collected and evaporated under reduced pressure. After removal of the water, [Hmim][HSO_4] was recovered.

Spiro[dibenzo[*a,i*]-xanthene-14,3'-indoline]-2',8,13-trione (5a): Red power, mp 365-366 °C; IR (KBr) ν 3302, 1807, 1679, 1629, 1573, 1518, 1491, 1355, 1304, 1271, 1249, 1116, 1075, 982, 809, 758, 719; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.92 (s, 1H), 8.11-7.96 (m, 3H), 7.78-7.64 (m, 5H), 7.46-7.25 (m, 4H), 6.94 (t, 1H, J = 7.6 Hz), 6.71 (d, 1H, J = 7.6 Hz); MS (ESI): *m/z* 430 $[M+H]^+$; Anal. calcd for $C_{28}H_{15}NO_4$: C 78.31, H 3.52, N 3.26; found: C 78.12, H 3.60, N 3.20.

5'-Chlorospiro[dibenzo[*a,i*]-xanthene-14,3'-indoline]-2',8,13-trione (5b): Red power, mp 392-393 °C; IR (KBr) ν 3280, 1802, 1679, 1628, 1562, 1504, 1355, 1299, 1248, 1122, 983, 811, 717; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.06 (s, 1H), 8.11-7.97 (m, 3H), 7.80-7.68 (m, 5H), 7.44-7.37 (m, 4H), 6.65 (s, 1H); MS (ESI): *m/z* 464 $[M+H]^+$; Anal. calcd for $C_{28}H_{14}ClNO_4$: C 72.50, H 3.04, N 3.02; found: C 72.61, H 3.11, N 3.00.

5'-Methylspiro[dibenzo[*a,i*]-xanthene-14,3'-indoline]-2',8,13-trione (5c): Purple power, mp 382-383 °C; IR (KBr) ν 3292, 2940, 2874, 1791, 1680, 1625, 1573, 1502, 1303, 1247, 1125, 984, 808, 720; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.90 (s, 1H), 8.09-7.95 (m, 3H), 7.77-7.67 (m, 4H), 7.56 (d, 1H, J = 8.0 Hz), 7.43-7.33 (m, 3H), 7.09 (d, 1H, J = 7.6 Hz), 6.61 (s, 1H), 2.05 (s, 3H); MS (ESI): *m/z* 444 $[M+H]^+$; Anal. calcd for $C_{29}H_{17}NO_4$: C 78.55, H 3.86, N 3.16; found: C 78.25, H 3.90, N 3.10.

5'-Florospiro[dibenzo[*a,i*]-xanthene-14,3'-indoline]-2',8,13-trione (5d): Red power, mp 389-390 °C; IR (KBr) ν 3352, 1808, 1678, 1627, 1527, 1497, 1355, 1307, 1240, 1158, 1008, 985, 809, 716; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.01 (s, 1H), 8.11-8.05 (m, 3H), 7.80-7.67 (m, 5H), 7.43-7.20 (m, 4H), 6.51 (s, 1H); MS (ESI): *m/z* 448 $[M+H]^+$; Anal. calcd for $C_{28}H_{14}FNO_4$: C 75.17, H 3.15, N 3.13; found: C 75.20, H 3.10, N 3.08.

5'-Bromospiro[dibenzo[*a,i*]-xanthene-14,3'-indoline]-2',8,13-trione (5e): Red power, mp 379-380 °C; IR (KBr) ν 3360, 1809, 1679, 1626, 1502, 1355, 1304, 1248, 1162, 982, 804, 712; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.06 (s, 1H), 8.10-7.97 (m, 3H), 7.90-7.62 (m, 5H), 7.51-7.37 (m, 4H), 6.77 (s, 1H); MS (ESI): *m/z* 508 $[M+H]^+$; Anal. calcd for $C_{28}H_{14}BrNO_4$: C 66.16, H 2.78, N 2.76; found: C 66.09, H 2.62, N 2.70.

1'-Methylspiro[dibenzo[*a,i*]-xanthene-14,3'-indoline]-2',8,13-trione (5f): Orange red power, mp 388-389 °C; IR (KBr) ν 2920, 2842, 1725, 1661, 1635, 1613, 1575, 1491, 1468, 1337, 1293, 1249, 1227, 1080, 1025, 982, 732; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.38 (d, 1H, J = 7.6 Hz), 8.12-7.77 (m, 5H), 7.43-7.25 (m, 6H), 7.07 (d, 1H, J = 7.2 Hz), 6.91-6.89 (m, 1H), 1.23 (s, 3H); MS (ESI): *m/z* 444 $[M+H]^+$; Anal. calcd for $C_{29}H_{17}NO_4$: C 78.55, H 3.86, N 3.16; found: C 78.42, H 3.72, N 3.13.

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