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Synthesis of symmetrical and unsymmetrical 3,3-di(indolyl)indolin-2-ones under controlled catalysis of ionic liquids

Kurosh Rad-Moghadam *, Masoumeh Sharifi-Kiasaraie, Homayun Taheri-Amlashi

Chemistry Department, University of Guilan, PO Box 41335-19141, Rasht, Iran

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ABSTRACT

Three ionic liquids, [BMIM][BF_4] doped with 60 mol % of LiCl ([BMIM][BF_4]–LiCl), *N*,*N*,*N*,*N*-tetramethylguanidinium trifluoroacetate (TMGT), and *N*,*N*,*N*,*N*-tetramethylguanidinium triflate ($TMGT_f$) were found useful as catalyst solvents for controlled 3-indolylation of isatins. Our investigation revealed that the reaction between isatin and indoles in [BMIM][BF_4]–LiCl or $TMGT_f$ media stops at the step of addition of the two components providing 3-indolyl-3-hydroxyindolin-2-ones while the ionic liquid TMGT runs the reaction further through accompanying Friedel–Crafts substitution to afford symmetrical 3,3-di(indol-3-yl)indolin-2-ones. To take advantage of the difference between the effects of these ionic liquids on the reaction progress, we planned a two-step protocol for the efficient synthesis of unsymmetrical 3,3-di(indol-3-yl)indolin-2-ones.

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1. Introduction

The versatile properties and the variety of available ionic liquids have made them promising substances for application in most chemistry areas.[1–3] Ionic liquids are new generation solvents composed of bulky organic cations having liquid range at/or close to room temperature, hence they are well positioned to fill the polarity gap between molecular liquids and the molten metal salts. The unique nature of ionic liquids allows virtually all possible interactions between the solutes and the ions thus have an ability to dissolve both organic and inorganic materials. On other hand, the high polarity of ionic liquids ensures immiscibility with many organic solvents, offering unique opportunities for phase separation and recycling. An important feature of ionic liquids is the possibility to tune their chemical properties and also to adjust their solubility to enable phase separation. Today, ionic liquids have been shown to be more than simple solvents, showing significant roles in controlling reactions as catalysts.[4,5] The early use of ionic liquids as catalysts was merely based on their role as polar media to facilitate organic reactions having polar transition states. The application now is extended by the so-called task-specific ionic liquids either through immobilization of the effective ionic catalysts in ionic liquids[6,7] or by incorporating a functional group responsible for catalysis in their ionic partners.[8–10] Synthesis by the aid of immobilized metal catalysts in ionic liquids[11,12] recently has received considerable attention because such 'liquid phase' synthesis retains the advantages of homogenous catalysis, and still permits the fairly facile purification of the products and recycling of the catalysts.

In continuation of our studies directed toward the use of ionic liquids as catalysts in synthesis of organic compounds,[13] herein we describe the efficiencies of three ionic liquids, [BMIM][BF_4] doped with 60 mol % of LiCl ([BMIM][BF_4]–LiCl), *N*,*N*,*N*,*N*-tetramethylguanidinium trifluoroacetate (TMGT), and *N*,*N*,*N*,*N*-tetramethylguanidinium triflate ($TMGT_f$) for the promotion of the reaction between isatin and indoles providing the catalytic controlled syntheses of 3-(indol-3-yl)-3-hydroxyindolin-2-ones and symmetrical or unsymmetrical 3,3-di(indol-3-yl)indolin-2-ones.

Isatin is a privileged lead molecule for designing potential bioactive agents, and its derivatives have been shown to possess a broad spectrum of bioactivity as many of which were assessed anti-HIV,[14] antiviral,[15] anti-tumor,[16–18] antifungal,[19,20] anti-angiogenic,[21] anticonvulsants,[22] anti-Parkinson's disease therapeutic,[23] and effective SARS coronavirus 3CL protease inhibitor.[24] These interesting properties prompted many efforts toward the synthesis and pharmacological screening of isatin derivatives. During these investigations, the indolin-2-one (oxindole) moiety has been recognized as a biologically active framework.[25,26] Oxindole is an integral constituent of many natural products.[27–31] Thus, it is not surprising that access to several members of this class may be the goal of many research laboratories. Oxindole derivatives have been prepared by the reaction of isatin or its derivatives with barbituric acid,[32] aromatics in triflic acid,[33] pyrazolones,[34] and other routes.[35–38] The 3,3-di(indol-3-yl)indolin-2-ones can be formed by the reaction of isatin and indoles in acidic conditions and several methods have been

* Corresponding author. Fax: +98 131 3220066.
E-mail address: radmm@guilan.ac.ir (K. Rad-Moghadam).

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developed for the synthesis of these compounds.[39–41] On the other hand, a number of oxindole alkaloids having a hydroxyl substituent at the C-3 position possess various bioactivities,[42,43] and were synthesized by a variety of methods.[38,44,45]

2. Result and discussion

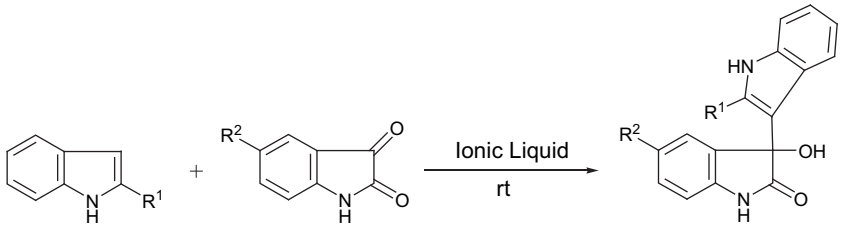
The 3-indolylation of isatin, which was found very sluggish in nature is essentially a Friedel–Crafts reaction. This recognition implies that the reaction could be assisted by enhancing the nucleophilic character of indoles in basic media, or by activating the carbonyl group of isatin with the aid of acidic species. In this view, we envisaged that the acid–base guanidinium ionic liquids could be suitable choices for performing the dual role. Our initial trials on the model reaction between indole and isatin in $TMGT_f$ was very encouraging as it proceeds smoothly at room temperature and stops at the stage of monoindolylation of isatin to afford 3-(indol-3-yl)-3-hydroxyindolin-2-one **3a** in fairly high yield. We have also performed the model reaction in either of the neutral ionic liquids, [BMIM]Cl and $[BMIM]BF_4$ or in the absence of ionic liquids to respond the issue if the high polarity of $TMGT_f$ is responsible for catalysis of the reaction. Of note, the model reaction has not proceeded in either of the above imidazolium ionic liquids or absence of them, confirming the functional role of $TMGT_f$ in catalysis of the reaction. To learn more about this function and on expectation that Li^+ could play the same role as H^+ in $TMGT_f$ we intended to test our model reaction in $[BMIM]BF_4$ doped with LiCl. As expected, the LiCl contained in $[BMIM]BF_4$ efficiently catalyzed the addition of indole onto isatin to provide 3-(indol-3-yl)-3-hydroxyindolin-2-one **3a** in a few minutes (Table 1).

Table 2
Synthesis of 3-(indol-3-yl)-3-hydroxyindolin-2-ones **3a–f** in $TMGT_f$ or $[BMIM][BF_4]$–LiCl ionic liquids

Entry	R^1	R^2	Product	Yield (%)	
				$[BMIM]BF_4$–LiCl	$TMGT_f$
1	H	H	**3a**	90	92
2	Me	H	**3b**	92	93
3	H	Br	**3c**	88	89
4	Me	Br	**3d**	90	87
5	H	F	**3e**	89	90
6	Me	F	**3f**	91	89

out in *N*,*N*,*N*,*N*-tetramethylguanidinium trifluoroacetate (TMGT), in place of $TMGT_f$, at room temperature. Monitoring of this reaction by TLC revealed a rather slow disappearance of the reactants, compared to the reaction in $TMGT_f$ or $[BMIM]BF_4$–LiCl, and still signifying an efficient conversion giving both 3-(indol-3-yl)-3-hydroxyindolin-2-one **3a** and 3,3-di(indol-3-yl)indolin-2-one **4a** in about an hour. Formation of 3,3-di(indol-3-yl)indolin-2-one **4a** as a by-product obviously accounts for the capability of TMGT to catalyze the Friedel–Crafts reaction between 3-(indol-3-yl)-3-hydroxyindolin-2-one **3a** and another indole molecule, meanwhile showing a need for optimization of conditions to gain better yield of **4a**. In order to optimize the reaction conditions, we performed the model reaction using different quantities of reactants and the ionic liquid. The best results were obtained with 1:2 mmol ratios of isatin and indoles in the presence of 1 mL of TMGT at room temperature. Therefore, we set out a method comprising the room temperature reaction of a 2:1 mixture of indole **1** and isatin **2** without using any solvent or additional catalyst in TMGT and

Table 1
Optimization of reaction conditions



1 **2** **3**

Entry	R^1	R^2	Ionic liquid	Product	Reaction time	Yield (%)
1	H	H	[BMIM]Cl	—	12 h	—
2	H	H	$[BMIM]BF_4$	—	12 h	—
3	H	H	$[BMIM]BF_4$–LiCl	**3a**	20 min	90
4	H	H	$TMGT_f$	**3a**	10 min	92
5	Me	H	[BMIM]Cl	—	12 h	—
6	Me	H	$[BMIM]BF_4$	—	12 h	—
7	Me	H	$[BMIM]BF_4$–LiCl	**3b**	20 min	92
8	Me	H	$TMGT_f$	**3b**	10 min	93

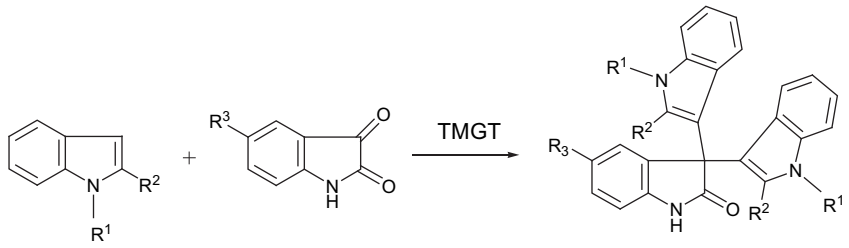
Several indoles and isatin derivatives, having electron donor and electron withdrawing substituents, likewise underwent the same reaction efficiently in both ionic liquids, $TMGT_f$ and $[BMIM]BF_4$–LiCl.

The results are summarized in Table 2. All the compounds **3a–f** are formed solely under these conditions and were not contaminated with the production of 3,3-di(indol-3-yl)indolin-2-ones **4** even when 3 equiv of indoles were employed in the reactions.

Delighted by this result, we intended to examine the effect of another guanidinium ionic liquid. For this purpose the reaction involving a 1:1 mmol ratio of isatin and indole was similarly carried thereby 3,3-di(indol-3-yl)indolin-2-ones **4a–f** were obtained in fairly high yields (Table 3). Here again both electron donor as well as electron withdrawing substituents exert no considerable effects on reactivity of reactants under catalysis of TMGT.

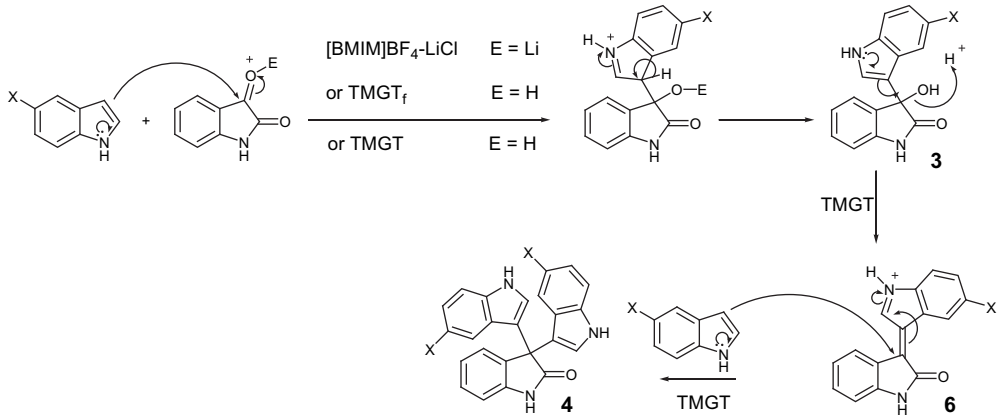
The condensation of indoles with isatin derivatives is better rationalized by an initial nucleophilic addition of the indole onto the ketonic carbonyl group of isatin to yield the corresponding 3-(indol-3-yl)-3-hydroxyindolin-2-one **3**. Dehydration of this adduct gives the intermediate **6**, which subsequently undergoes nucleophilic addition of the second indole molecule to provide the final products 3,3-di(indol-3-yl)indolin-2-ones **4** (Scheme 1).

Table 3
Synthesis of symmetrical 3,3-di(indolyl)indolin-2-ones from indoles and isatin derivatives in TMGT



1 **2** **4**

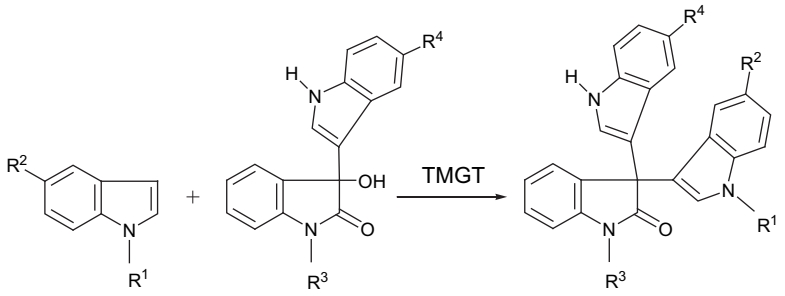
Entry	R^1	R^2	R^3	Product	Yield (%)
1	H	H	H	**4a**	93
2	Me	H	OMe	**4b**	91
3	Me	H	Br	**4c**	86
4	H	Me	H	**4d**	90
5	Me	H	NO_2	**4e**	88



Scheme 1. Proposed mechanism for the reaction between isatin and indole derivatives in the ionic liquids.

In the next phase of this investigation we planned to take advantage of the difference between catalytic activities of TMGT and $TMGT_f$ for the synthesis of unsymmetrical 3,3-di(indol-3-yl)indolin-2-ones in a more controlled manner. In this protocol the initially synthesized 3-(indol-3-yl)-3-hydroxyindolin-2-ones **3**, on reaction of an isatin derivatve with an indole in $TMGT_f$ or [BMIM]BF_4–LiCl ionic liquids, was treated with 1 equiv of another indole derivate in TMGT to give the desired unsymmetrical 3,3-di(indol-3-yl)indolin-2-one **5**. The results of the application of this procedure are summarized in Table 4.

Table 4
Synthesis of unsymmetrical 3,3-di(indolyl)indolin-2-ones from indoles and isatin in TMGT



1 **3** **5**

Entry	R^1	R^2	R^3	R^4	Yield (%)	Product
1	H	H	H	H	**5a**	90
2	H	H	H	CN	**5b**	88
3	H	H	H	Br	**5c**	88
4	H	Br	Me	H	**5d**	87
5	Me	H	H	H	**5e**	91

3. Conclusion

We have demonstrated the application of three ionic liquids in the synthesis of 3-(indol-3-yl)-3-hydroxyindolin-2-ones, symmetrical and unsymmetrical 3,3-di(indol-3-yl)indolin-2-ones of biological interests at room temperature. The reaction of an indole and an isatin derivative even in 3:1 mole ratio under catalysis of either $TMGT_f$ or [BMIM]BF_4–LiCl ionic liquids gave solely the 1:1 adduct, 3-(indol-3-yl)-3-hydroxyindolin-2-ones **3a**–**f**, in fairly high yields at room temperature, while similar reaction in TMGT favored to form solely symmetrical 3,3-di(indol-3-yl)indolin-2-ones **4a**–**e**. We have also devised the reaction between the adducts **3** and indoles in TMGT to synthesize some unsymmetrical 3,3-di(indol-3-yl)indolin-2-ones **5a**–**e** at room temperature. Experimental simplicity associated with the high yield of products, recyclability of the ionic liquids, and short reaction times render the methods presented here highly competitive compared to existing procedures. We believe that the simple and novel methods presented here could be of broad interest for synthetic and medicinal chemists.

4. Experimental section

4.1. General

All of the solvents and reagents were purchased from Fluka or Merck chemical companies. Melting points were measured on an Electrothermal apparatus and are uncorrected. IR spectra were obtained in KBr discs on a Shimadzu IR-470 spectrometer. ^1H and ^{13}C NMR spectra were measured with Brucker DRX-500, DRX-400 or DRX-300 AVANCE spectrometers. Chemical shifts of ^1H and ^{13}C NMR spectra were expressed in parts per million downfield from tetramethylsilane. Mass spectra were recorded on a Shimadzu QP1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N were performed using a Foss Heraus CHN-O-rapid analyzer.

4.2. Procedure for preparation of [BMIM]BF_4–LiCl

1-Methylimidazole (5.1 g, 62.1 mmol) was added to 32 mL of 1-chlorobutane. The mixture was heated to reflux for 24 h and then cooled to room temperature, the obtained oily product was separated from reaction mixture by decanting, washed with EtOAc (2× 20 mL), and the solvent of the collected organic phase was removed under reduced pressure to give 1-butyl-3-methylimidazolium chloride ([BMIM]Cl). In second step, to [BMIM]Cl (9.3 g, 53 mmol) dissolved in anhydrous acetone (40 mL) was added $LiBF_4$ (5 g, 53 mmol). The mixture was then stirred for 48 h at room temperature to get a solution and then stored at 4 °C over 2 days in refrigerator giving the excess of the dissolved LiCl crystals to precipitate. After separation of the precipitated LiCl crystals (0.87 g, 20.5 mmol) the solvent of the filtered solution was removed under reduced pressure thereby the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate doped with 60 mol % of LiCl ([BMIM]BF_4–LiCl) was obtained as a yellow oil.

4.3. General procedure for preparation of 3-(indol-3-yl)-3-hydroxyindolin-2-ones (3a–f)

A mixture of the indole (1 mmol) and an isatin derivative (1 mmol) was added to a vial containing a magnetic stir bar and the ionic liquid ($TMGT_f$ or [BMIM][BF_4]–LiCl, 1 mL). The reaction mixture was sealed and stirred at room temperature until disappearance of the starting materials (20 min for [BMIM][BF_4]–LiCl, 10 min for $TMGT_f$), as monitored by TLC on silica gel using 1:2 mixture of ethyl acetate/*n*-hexane. After completion of the reaction, the residue was washed with 2×15 mL of cold water to extract the ionic liquids. The solid residues were recrystallized from ethanol (95.5%) to afford pure products **3a**–**f**. The ionic liquids were recovered from the aqueous extracts by evaporation of water in reduced pressure and reused in the next cycles. All the known products have spectral and physical data consistent with those reported in literatures as well as the samples prepared from previously reported methods.

*4.3.1. 3-Hydroxy-3-(1H-indol-3-yl)indolin-2-one (**3a**).* White solid (0.243 g, 92%), mp 293–295 °C, lit.[44] mp 294–296 °C; ν_{max} (KBr) 3457, 3261, 1702, 1618, 1476, 1182 cm^{-1}; δ_H (300 MHz, DMSO) 6.32 (1H, s, O*H*), 6.85 (1H, t, *J* 8.0 Hz), 6.90 (1H, d, *J* 7.6 Hz), 6.96 (1H, t, *J* 6.7 Hz), 7.02 (1H, t, *J* 7.0 Hz), 7.06 (1H, d, *J* 2.6 Hz), 7.23 (1H, d, *J* 6.0 Hz), 7.25 (1H, t, *J* 6.5 Hz), 7.32 (1H, d, *J* 8.2 Hz), 7.34 (1H, d, *J* 9.4 Hz), 10.32 (1H, s, amidic N–*H*), 10.97 (1H, br s, N–*H*).

*4.3.2. 3-Hydroxy-3-(2-methyl-1H-indol-3-yl)indolin-2-one (**3b**).* Dark red solid (0.259 g, 93%), mp 181–183 °C, lit.[44] mp 178–180 °C; ν_{max} (KBr) 3398, 3352, 3297, 1705, 1617 cm^{-1}; δ_H (300 MHz, DMSO) 2.41 (3H, s, CH_3), 6.27 (1H, s, O*H*), 6.73 (1H, t, *J* 7.5 Hz), 6.89–6.97 (4H, m), 7.18–7.26 (3H, m), 10.34 (1H, s, amidic N–*H*), 10.87 (1H, br s, N–*H*).

*4.3.3. 5-Bromo-3-hydroxy-3-(1H-indol-3-yl)indolin-2-one (**3c**).* White solid (0.306 g, 89%), mp 200 °C (dec). Found: C, 56.16; H, 3.31; N, 8.08. $C_{16}H_{11}BrN_2O_2$ requires C, 56.00; H, 3.23; N, 8.16%; ν_{max} (KBr) 3457, 3261, 1703, 1615, 1472, 1168 cm^{-1}; δ_H (300 MHz, DMSO) 6.55 (1H, br s, O*H*), 6.88–6.96 (2H, m), 7.05 (1H, t, *J* 7.7 Hz, 5′-H), 7.12 (1H, d, *J* 2.3 Hz, 2′-*H* of indole), 7.33 (1H, d, *J* 2.0 Hz, 4-*H*), 7.36 (2H, d, *J* 8.3 Hz), 7.44 (1H, dd, *J* 8.2 and 2.0 Hz, 6-*H*), 10.30 (1H, br, N–*H*), 11.07 (1H, s, N–*H*); δ_C (100.62 MHz, DMSO) 75.4 (*C*-3), 112.1, 112.3, 113.8, 115.1, 119.2, 120.5, 121.7, 124.1, 125.2, 127.8, 132.2, 136.3, 137.3, 141.4, 178.4 (*C*═O).

*4.3.4. 5-Bromo-3-hydroxy-3-(2-methyl-1H-indol-3-yl)indolin-2-one (**3d**).* Brown solid (0.321 g, 90%), mp 136–138 °C. Found: C, 57.22; H, 3.72; N, 7.68. $C_{17}H_{13}BrN_2O_2$ requires C, 57.17; H, 3.67; N, 7.84%; ν_{max} (KBr) 3387 (br), 1721, 1615, 1465, 1178 cm^{-1}; δ_H (300 MHz, DMSO) 2.41 (3H, s, CH_3), 6.47 (1H, s, O*H*), 6.77 (1H, t, *J* 7.5 Hz, 5′-*H*), 6.86–6.98 (3H, m,), 7.21 (1H, d, *J* 8.1 Hz, 7-*H*), 7.24 (1H, d, *J* 2.0 Hz, 4-*H*), 7.41 (1H, dd, *J* 8.1 and 2.0 Hz, 6-*H*), 10.54 (1H, s, amidic N–*H*), 10.95 (1H, s, N–*H*); δ_C (100.62 MHz, DMSO) 13.7 (*C*H_3), 76.4 (*C*-3), 109.1, 110.9, 112.3, 113.8, 118.9, 119.3, 120.4, 126.8, 127.9, 132.1, 134.0, 135.3, 137.0, 141.3, 178.6 (*C*═O).

*4.3.5. 5-Fluoro-3-hydroxy-3-(1H-indol-3-yl)indolin-2-one (**3e**).* White solid (0.254 g, 90%), mp 194–196 °C, lit.[44] mp 196–198 °C; ν_{max} (KBr) 3425, 3355, 1720, 1623, 1484, 1189 cm^{-1}; δ_H (300 MHz, DMSO) 6.50 (1H, br s, O*H*), 6.80–6.91 (2H, m), 7.01–7.12 (3H, m), 7.11 (1H, br s, 2′-*H* of indole), 7.35 (2H, t, *J* 7.8 Hz), 10.38 (1H, s, amidic N–*H*), 11.04 (1H, s, N–*H*); δ_C (75.47 MHz, DMSO) 75.6 (*C*-3), 110.9 (d, $^3J_{C-F}$ 7.9 Hz, *C*-7), 112.0, 112.7 (d, $^2J_{C-F}$ 25.0 Hz), 115.2, 115.7 (d, ^2J 23.0 Hz), 119.0, 120.6, 121.6, 124.0, 125.2, 135.6 (d, $^3J_{C-F}$ 7.6 Hz, *C*-3*a*), 137.2, 138.2, 156.9 (d, $^1J_{C-F}$ 24.8 Hz, *C*-5), 178.8 (*C*═O); *m*/*z* (EI) 282 (24, M^+), 253 (14, M^+–[HC═O]), 237 (100, M^+–[OH+C═O]), 144 (14), 117 (45), 89 (13).

*4.3.6. 5-Fluoro-3-hydroxy-3-(2-methyl-1H-indol-3-yl)indolin-2-one (**3f**).* White solid (0.269 g, 91%), mp 212–213 °C, lit.[44] mp 212–214 °C; ν_{max} (KBr) 3340, 3199, 1713, 1625, 1485, 1461, 1188 cm^{-1}; δ_H (300 MHz, DMSO) 2.42 (3H, s, CH_3), 6.43 (1H, br s, O*H*), 6.75 (1H, t, *J* 7.2 Hz, 5′-*H*), 6.90–7.00 (4H, m), 7.08 (1H, t, *J* 8.1 Hz, 6-*H*), 7.20 (1H, d, *J* 7.8 Hz, 4-*H*), 10.40 (1H, s, amidic N–*H*), 10.93 (1H, s, N–*H* of indole); δ_C (75.47 MHz, DMSO) 13.8 (*C*H_3), 76.6 (*C*-3), 109.2, 110.8, 111.0 (d, $^3J_{C-F}$ 7.8 Hz, C-7), 112.8 (d, $^2J_{C-F}$ 24.0 Hz), 115.7 (d, $^2J_{C-F}$ 22.7 Hz), 118.8, 119.3, 120.4, 126.8, 134.1, 135.3, 136.4 (d, $^3J_{C-F}$ 7.7 Hz,

C-3a), 138.2, 158.6 (d, $^1J_{C-F}$ 252 Hz, C-5), 179.1 (*C*=O); *m*/*z* (EI) 296 (15, M^+), 288 (18), 251 (46, M^+−[OH+C=O]), 237 (58, 251−[CH_2]), 130 (100, *N*-methylindole), 109 (60), 82 (60).

4.4. Synthesis of symmetrical 3,3-di(indol-3-yl)indolin-2-ones (4a–e)

A mixture of the indole **1** (1 mmol) and an isatin derivative **2** (0.5 mmol) was added to a vial containing a magnetic stir bar and the ionic liquid (TMGT, 1 mL). The reaction mixture was sealed and stirred at room temperature until the isatin derivative was completely consumed (about 1 h, as monitored by TLC on silica gel using a 4:3 mixture of ethyl acetate/*n*-hexane). After completion of the reaction, the resulting paste was washed with 2×15 mL of cold water to extract the ionic liquid. The remained crude products **4a**–**e** were crystallized from ethanol (95.5%). To recover the ionic liquid, the aqueous filtrate was evaporated under reduced pressure. TMGT, which remained as nonvolatile oil in the evaporating vessel was collected and reused. All the novel products were characterized by their IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data, as well as elemental analysis. Partial assignments of the spectral data are given in the following sections.

*4.4.1. 3,3-Di(1H-indol-3-yl)indolin-2-one (**4a**).* White solid (0.338 g, 93%), mp>300 °C, lit.[39] mp 311–313 °C; ν_{max} (KBr) 3420, 3300, 1704, 1610, 1105, 737 cm^{-1}; δ_H (500 MHz, DMSO) 6.79 (2H, t, *J* 7.7 Hz), 6.84 (2H, d, *J* 2.2 Hz, 2′-*H* of indoles), 6.92 (1H, t, *J* 7.5 Hz), 6.97–7.02 (3H, m), 7.22 (4H, d, *J* 7.8 Hz), 7.35 (2H, d, *J* 8.1 Hz), 10.58 (1H, s, amidic *N*–*H*), 10.94 (2H, br s, N–*H*); δ_C (125.8 MHz, DMSO) 53.4 (*C*-3), 110.4, 112.4, 115.2, 119.1, 121.6, 121.8, 122.3, 125.1, 125.8, 126.6, 128.7, 135.5, 137.8, 142.2, 179.6 (*C*=O); *m*/*z* (EI) 363 (57, M^+), 334 (69, M^+−[HC=O]), 248 (64, M^+−[indole]), 219 (95, 334−[indole]), 117 (64), 86 (100).

*4.4.2. 5-Methoxy-3,3-di(1-methyl-1H-indol-3-yl)indolin-2-one (**4b**).* Pale pink solid (0.383 g, 91%), mp 279–281 °C. Found: C, 77.02; H, 5.59; N, 9.89. $C_{27}H_{23}N_3O_2$ requires C, 76.94; H, 5.50; N, 9.97%; ν_{max} (KBr) 3200, 3100, 1702, 1603, 1486, 1200, 740 cm^{-1}; δ_H (500 MHz, DMSO) 3.61 (3H, s, O*CH*$_3$), 3.70 (6H, s, N–*CH*$_3$), 6.81–6.87 (4H, m), 6.92 (1H, d, *J* 7.8 Hz, 6-*H*), 6.93 (2H, s, 2′-*H* of indoles), 7.09 (2H, t, *J* 7.4 Hz), 7.28 (2H, d, *J* 8.0 Hz), 7.38 (2H, d, *J* 8.3 Hz), 10.47 (1H, s, amidic N–*H*); δ_C (125.8 MHz, DMSO) 33.2 (N–*CH*$_3$), 53.7 (*C*-3), 56.2 (O–*CH*$_3$), 110.6, 110.8, 113.0, 114.3, 119.3, 121.8, 122, 126.9, 129.4, 135.5, 136.7, 138.2, 155.6 (*C*-5), 179.3 (*C*=O); *m*/*z* (EI) 421 (78, M^+), 407 (7, M^+−[CH_2]), 392 (100, M^+−[HC=O]), 348 (14), 291 (12, M^+−[*N*-methylindole]), 263 (16, 392−[*N*-methylindole]), 211 (10), 131 (10).

*4.4.3. 5-Bromo-3,3-di(1-methyl-1H-indol-3-yl)indolin-2-one (**4c**).* Pale pink solid (0.405 g, 86%), mp>300 °C. Found: C, 66.52; H, 4.36; N, 8.86. $C_{26}H_{20}BrN_3O$ requires C, 66.40; H, 4.28; N, 8.93%; ν_{max} (KBr) 3390, 3120, 3050, 1738, 1610, 1480, 1337, 1075, 739 cm^{-1}; δ_H (500 MHz, DMSO) 3.72 (6H, s, N–*CH*$_3$), 6.88 (2H, t, *J* 7.4 Hz), 7.01 (2H, s, 2′-H of indoles), 7.11 (2H, t, *J* 7.4 Hz), 7.20 (1H, d, *J* 8.6 Hz, 7-H), 7.25 (2H, d, *J* 8.0 Hz), 7.41 (2H, d, *J* 8.2 Hz), 7.99 (1H, s, 4-H), 8.24 (1H, d, *J* 8.6 Hz, 6-H), 11.35 (1H, s, amidic N–*H*); δ_C (125.8 MHz, DMSO) 33.2 (*CH*$_3$), 53.5 (*C*-3), 110.8, 112.6, 113.5, 114.1, 119.5, 121.6, 122.1, 126.7, 128.2, 129.4, 131.6, 137.7, 138.2, 141.5, 178.9 (*C*=O); *m*/*z* (EI) 471 (2, M^+, ^{81}Br), 470 (4), 469 (2, M^+, ^{79}Br), 468 (4), 442 (10), 411 (26), 285 (26), 223 (35), 149 (73), 57 (100).

*4.4.4. 3,3-Di(2-methyl-1H-indol-3-yl)indolin-2-one (**4d**).* White solid (0.352 g, 90%), mp>300 °C, lit.[39] mp 300–301 °C; ν_{max} (KBr) 3370, 3119, 3050, 1705, 1615, 740 cm^{-1}; δ_H (500 MHz, DMSO) 1.93 (3H, s, *CH*$_3$), 2.06 (3H, s, *CH*$_3$), 6.45 (1H, d, *J* 8.2 Hz), 6.60 (1H, t, *J* 7.1 Hz), 6.63 (1H, d, *J* 7.8 Hz), 6.69 (1H, d, *J* 8.0 Hz), 6.85 (1H, t, *J* 7.5 Hz), 6.88 (1H, t, *J* 7.1 Hz), 6.89 (1H, t, *J* 7.2 Hz), 6.94 (1H, d, *J* 7.7 Hz), 7.14 (1H, d, *J* 7.3 Hz), 7.20–7.23 (3H, m), 10.50 (1H, s, amidic N–*H*), 10.82 (1H, br s, N–*H*), 10.85 (1H, br s, N–*H*).

*4.4.5. 5-Nitro-3,3-di(1-methyl-1H-indol-3-yl)indolin-2-one (**4e**).* Pale brown solid (0.384 g, 88%), mp>300 °C. Found: C, 71.64; H, 4.73; N, 12.70. $C_{26}H_{20}N_4O_3$ requires C, 71.56; H, 4.62; N, 12.83%; ν_{max} (KBr) 3230, 3105, 3055, 1715, 1608, 1465, 1325, 1158, 730; δ_H (500 MHz, DMSO) 3.72 (6H, s, 2×*CH*$_3$), 6.89 (2H, t, *J* 7.5 Hz, 5′-*H* of indoles), 7.02 (2H, s, 2′-*H* of indoles), 7.11 (2H, t, *J* 7.5 Hz, 6′-*H* of indoles), 7.21 (1H, d, *J* 8.6 Hz, 7-*H*), 7.26 (2H, d, *J* 8.1 Hz), 7.40 (2H, d, *J* 8.2 Hz), 8.00 (H, s, 4-*H*), 8.25 (1H, d, *J* 8.6 Hz, 6-*H*), 11.36 (1H, s, amidic N–*H*); δ_C (125.8 MHz, DMSO) 33.2 (2×*CH*$_3$), 53.2 (*C*-3), 110.8, 110.9, 112.8, 119.6, 121.0, 121.4, 122.2, 126.4, 126.6, 129.6, 136.0, 138.3, 143.1, 148.6, 179.6 (*C*=O); *m*/*z* (EI) 436 (86, M^+), 422 (22, M^+−[CH_2]), 407 (100, M^+−[HC=O]), 393 (25, 422−[CH_2]), 361 (28), 306 (21, M^+−[*N*-methylindole]), 278 (22, 306−[HC=O]), 232 (18), 131 (33).

4.5. Synthesis of unsymmetrical 3,3-di(indol-3-yl)indolin-2-ones (5a–e)

A mixture of oxindoles **3a**–**f** (1 mmol) and an indole derivative (1 mmol) was added to a vial containing a magnetic stir bar and TMGT (1 mL). The reaction mixture was sealed and stirred at room temperature until the disappearance of the starting materials (1 h, monitored by TLC on silica gel using 4:3 mixture of ethyl acetate/*n*-hexane). After completion of the reactions, the residues were washed with 2×15 mL of cold water to extract TMGT. The remained crude products **5a**–**e** were recrystallized from ethanol (95.5%). TMGT was recovered from the aqueous extracts by evaporation of water in reduced pressure and reused in the next cycles. Partial assignment of spectral data to the structure of previously unreported products **5** is given in the following sections.

*4.5.1. 3,3-Di(1H-indol-3-yl)indolin-2-one (**5a**).* Compound **5a** is identical with **4a** (0.327 g, 90%).

*4.5.2. 3-(1H-Indol-3-yl)-3-(5-cyano-1H-indol-3-yl)indolin-2-one (**5b**).* Light pink solid (0.341 g, 88%), mp>300 °C. Found: C, 77.25; H, 4.17; N, 14.41. $C_{25}H_{16}N_4O$ requires C, 77.31; H, 4.15; N, 14.42%. ν_{max} (KBr) 3360, 3254, 3100, 2220, 1675, 1618, 1467, 1200, 740 cm^{-1}; δ_H (500 MHz, DMSO) 6.82 (1H, t, *J* 7.4 Hz), 6.91 (1H, d, *J* 1.8 Hz, 2′-*H*), 6.97 (1H, t, *J* 7.6 Hz), 7.02–7.04 (2H, m), 7.07 (1H, d, *J* 1.8 Hz, 2″-*H*), 7.15 (1H, d, *J* 8 Hz), 7.26 (2H, d, *J* 7.4 Hz), 7.35–7.42 (2H, m), 7.56 (2H, d, *J* 8.5 Hz), 7.72 (1H, s, 4′-*H*), 10.72 (1H, s, amidic N–*H*), 11.02 (1H, br s, N–*H*), 11.62 (1H, br s, N–*H*); δ_C (125.8 MHz, DMSO) 53.2 (*C*-3), 101.2, 110.7, 112.7, 114.1, 114.9, 116.3, 119.4, 120.8, 121.6, 122, 122.6, 124.5, 125.2, 125.8, 126.3, 126.4, 127.6, 127.7, 129.0, 134.7, 137.8, 139.7, 142.1, 179.4 (*C*=O); *m*/*z* (EI) 388 (44, M^+), 359 (57, M^+−[HC=O]), 334 (24), 273 (63, M^+−[indole]), 244 (75, 359−[indole]), 219 (45, 359−[5-cyanoindole]), 142 (44), 117 (100), 94 (66), 71 (42).

*4.5.3. 3-(1H-Indol-3-yl)-3-(5-bromo-1H-indol-3-yl)indolin-2-one (**5c**).* Pale brown solid (0.389 g, 88%), mp 284–286 °C. Found: C, 65.07; H, 3.73; N, 9.42. $C_{24}H_{16}BrN_3O$ requires C, 65.18; H, 3.64; N, 9.50%; ν_{max} (KBr) 3390, 3310, 3104, 3050, 1680, 1660, 1468, 1450, 1330, 1100, 740 cm^{-1}; δ_H (500 MHz, DMSO) 6.83 (1H, t, *J* 7.6 Hz), 6.90 (1H, d, *J* 1.6 Hz), 6.91 (1H, d, *J* 1.5 Hz), 6.96 (1H, t, *J* 7.6 Hz), 7.01–7.05 (2H, m), 7.16 (1H, d, *J* 8.6 Hz), 7.21 (2H, t, *J* 7.9 Hz), 7.25 (1H, t, *J* 7.6 Hz), 7.37 (2H, t, *J* 8.8 Hz), 7.48 (1H, s, 4′-*H*), 10.68 (1H, s, amidic N–*H*), 10.97 (1H, br s, N–*H*), 11.22 (1H, br s, N–*H*); δ_C (125.8 MHz, DMSO) 53.3 (*C*-3), 110.6, 111.8, 112.6, 114.6, 114.9, 115, 119.3, 121.1, 121.9, 122.5, 124.2, 124.4, 125.2, 125.8, 126.4, 126.7, 128.4, 128.9, 135, 136.6, 137.8, 142.2, 179.5 (*C*=O); *m*/*z* (EI) 443 (40, M^+, ^{81}Br), 441 (40,

M^+, ^{79}Br), 414 (43, 443−[HC═O]), 412 (42, 441−[HC═O]), 363 (49), 334 (62), 299 (25, 414−[indole]), 297 (20, 412−[indole]), 248 (74), 219 (100, 414−[5-bromoindole]), 195 (55), 193 (55), 117 (80).

*4.5.4. 1-Methyl-3-(1H-indol-3-yl)-3-(5-bromo-1H-indol-3-yl)indolin-2-one (**5d**).* Pale brown solid (0.397 g, 87%), mp>300 °C. Found: C, 65.67; H, 4.05; N, 9.28. $C_{25}H_{18}BrN_3O$ requires C, 65.81; H, 3.98; N, 9.20%; ν_{max} (KBr) 3350, 3106, 1662, 1604, 1460, 1445, 1087, 740 cm^{-1}; δ_H (500 MHz, DMSO) 3.27 (3H, s, N–C*H*$_3$), 6.81 (1H, t, *J* 7.5 Hz), 6.89 (1H, d, *J* 2.1 Hz), 6.90 (1H, d, *J* 2.1 Hz), 7.01–7.09 (3H, m), 7.14–7.20 (2H, m), 7.27 (1H, d, *J* 7.3 Hz), 7.30–7.37 (4H, m), 7.47 (1H, s, 4′-*H*), 11.00 (1H, br s, N–*H*), 11.24 (1H, br s, N–*H*); δ_C (125.8 MHz, DMSO) 27.1 (*C*H$_3$), 52.8 (*C*-3), 109.7, 111.8, 112.6, 114.6, 114.8, 119.4, 120.8, 122, 123.2, 123.5, 124.3, 124.4, 125.3, 125.4, 126.3, 126.7, 128.3, 129.1, 134.1, 136.6, 137.8, 143.6, 177.6 (C═O); *m*/*z* (EI) 457 (19, M^+, ^{81}Br), 456 (66), 455 (18, M^+, ^{79}Br), 454 (60), 429 (5, M^+−[C═O]), 428 (18, 456−[C═O]), 426 (17, 454−[C═O]), 414 (18, 428−[CH_2]), 392 (100), 377 (15, M^+−[Br]), 364 (75), 348 (23), 214 (22), 115 (36).

*4.5.5. 3-(1H-Indol-3-yl)-3-(1-methyl-1H-indol-3-yl)indolin-2-one (**5e**).* White solid (0.344 g, 91%), mp 299–301 °C, lit.[39] mp 298–300 °C; ν_{max} (KBr) 3310, 3190, 1683, 1615, 1469, 1330, 1100, 740 cm^{-1}; δ_H (500 MHz, DMSO) 3.70 (3H, s, C*H*$_3$), 6.80 (1H, t, *J* 7.5 Hz), 6.84 (1H, t, *J* 7.7 Hz), 6.87 (2H, s, 2-*H* of indoles), 6.93 (1H, t, *J* 7.4 Hz), 6.98–7.03 (2H, m), 7.08 (1H, t, *J* 7.4 Hz), 7.22–7.26 (4H, m), 7.36 (2H, t, *J* 8.4 Hz), 10.61 (1H, s, amidic N–*H*), 10.97 (1H, br s, N–*H*); δ_C (125.8 MHz, DMSO) 33.2 (*C*H$_3$), 53.4 (C-3), 110.4, 110.6, 112.5, 114.4, 115.1, 119.1, 119.2, 121.5, 121.8, 121.9, 122.0, 122.4, 125.2, 125.8, 126.5, 126.9, 128.7, 129.3, 135.4, 137.8, 138.2, 142.2, 179.5 (C═O); *m*/*z* (EI) 379 (4, M^+), 377 (90, M^+−2), 348 (100), 332 (13), 261 (13), 219 (21).

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