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[BMIM]OH: TASK-SPECIFIC IONIC LIQUID MEDIATED SYNTHESIS OF BISINDOLYLOXINDOLES, BISAZAINDOLYLOXINDOLES & BISPYRROLYLOXINDOLES

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Abstract: A simple, efficient and green method for the synthesis of bisindolyloxindoles & bisazaindolyloxindoles (**3, 5** & **7**) under task-specific ionic liquid ([Bmim]OH) mediated and catalyzed conditions is described involving reaction of isatin **1** with indole **2** / azaindole **4** / pyrrole **6** at 100 ^{O}C in about an hr, giving the products in yields of 85-90%. This method is of significant value due to the eco-friendly nature of ionic liquid and non usage of separate catalyst to drive the reaction forward.

Keywords: [Bmim]OH, bisindolyl, bisazaindolyloxindoles, Eco-friendly synthesis

Introduction

Bisindolyl derivatives have been drawing the attention of synthetic organic chemists due to their wide spectrum of biological properties[I]. 3,3-Diaryloxindoles are known to exhibit a wide range of biological activities such as antibacterial[IIa], antiprotozoal[IIb], anti-inflammatory[IIc] and anti-cancer activity[IId]. Generally, 3,3-diaryloxindoles are reported to have been prepared by acid-catalyzed condensation of arenes with isatin[III,IV]. Recently, isatin-dibarbiturates have been prepared from isatin and barbituric acid also under acidic conditions[V]. Thus, the development of new and simple synthetic methods for the preparation of bisindolyloxindoles is an interesting synthetic challenge.

Ionic liquids as catalysts[VI] and /or media[VII] in reactions have been widely used in organic transformations due to their advantages such as good solvating ability, negligible vapor pressure, high polarity and ease of work-up. [Bmim]OH (1-butyl-3-methylimidazolinium hydroxide) is one such task-specified ionic liquid which acts as reaction medium as well as a basic catalyst and has got varied applications[VIII] in the field of synthetic methodology development.

In view of our continued interest in indoles[IX] and the development of green procedures for the synthesis of diverse heterocyclic compounds of biological significance, we now report a simple and efficient method for the synthesis of bisindolyl oxindoles by condensing isatin with indole/azaindole/pyrroles to afford 3,3-bisindolyl- 3,3-bisazaindolyl and 3,3-bispyrrolyloxindoles using [Bmim]OH as a task-specific ionic liquid.

Experimental section

Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. Thin-layer chromatography (TLC) was performed on silica gel G coated plates using ethyl acetate-hexane (20:80) mixture as elluent and spotting was done using iodine vapour or UV light. IR spectra were recorded using Jasco FT-IR 5300, ^{1}H NMR on Varian 400 MHz instrument and mass spectra on an Agilent LC-MS instrument giving only $M^{+\cdot}$ values in Q+1 mode.

General procedure for the synthesis of 3a-3h, 5a-5e and 7a-7c:

A mixture of appropriate isatin (**1**, 1.0 mmol), indole (**2**, 2.0 mmol) / azaindole (**4**, 2.00 mmol) / pyrrole (**6**, 2.00 mmol) and [Bmim]OH (10 ml) was heated at 100 ^{0}C until the completion of reaction as checked by TLC. To the resulting oily reaction mixture was added ethanol (10 ml) to force out the crude product from the polar ionic liquid reaction medium. The separated solid mass was collected by filtration and dried in oven to obtain crude **3/5/7**. The latter, were recrystallized from a suitable solvent to get the pure **3/5/7**. The filterate consisting of the ionic liquid and ethanol was rotary evaporated to remove ethanol and the recovered ionic liquid reused for subsequent reactions. To compensate for the loss of some ionic liquid during the work up procedure, an amount (5 ml) of fresh [Bmim]OH was added after 4 runs.

Characterization of data

3a (R= R^1= H): MP: > 250 ^{o}C (Lit [IId] MP: 311-313 ^{o}C); Yield: 0.32 gr (85%) ; IR (KBr): 3425, 3375, 3120 (-NH), 1709 cm^{-1} (-C=O); ^{1}H NMR (DMSO-d_6) δ 6.79-8.15 (m, 14H, 10H indolyl+4H isatin protons), 10.70 (s, 1H, -NH, D_2O exch.), 11.57(s, 2H, -NH, D_2O exch.); m/z: [m$^{\cdot+}$+1]: 364.

3b (R= F, R^1= H): MP: > 250 ^{o}C; Yield: 0.34 gr (89%); IR (KBr): 3415, 3342, 3095 (-NH), 1720 cm^{-1} (-C=O); ^{1}H NMR (DMSO-d_6) δ 6.81-7.37((m, 13H, 10H indolyl+3H isatin protons), 10.63 (s, 1H, -NH, D_2O exch.), 11.00 (s, 2H, -NH, D_2O exch.); m/z: [M$^{\cdot+}$+1]: 382.

3c (R= Cl, R^1= H): MP: > 250 ^{o}C; Yield: 0.35 gr (87%); IR (KBr): 3425, 3405, 3105 (-NH), 1715 cm^{-1} (-C=O); ^{1}H NMR (DMSO-d_6) δ 6.78-7.52((m, 13H, 10H indolyl+3H isatin protons), 10.24 (s, 1H, -NH, D_2O exch.), 11.04 (s, 2H, -NH, D_2O exch.); m/z: [M$^{\cdot+}$+1]: 398.

3d (R= Br, R^1= H):): MP: > 250 ^{o}C (Lit [2d] MP: 310-311 ^{o}C); Yield: 0.38 gr (86%); IR (KBr): 3390, 3305, 3140 (-NH), 1698 cm^{-1} (-C=O); ^{1}H NMR (DMSO-d_6) δ 6.80-7.43((m, 13H, 10H indolyl+3H isatin protons), 10.76 (s, 1H, -NH, D_2O exch.), 11.02 (s, 2H, -NH, D_2O exch.); m/z: [M$^{\cdot+}$+1]: 442.

3e (R= I, R^1= H): MP: > 250 ^{o}C; Yield: 0.35 gr (90%); IR (KBr): 3425, 3365, 3136 (-NH), 1706 cm^{-1} (-C=O); ^{1}H NMR (DMSO-d_6) δ 6.86-7.52((m, 13H, 10H indolyl+3H isatin protons), 10.76 (s, 1H, -NH, D_2O exch.), 11.02 (s, 2H, -NH, D_2O exch.); m/z: [M$^{\cdot+}$+1]: 490.

3f (R= H, R^1= NO2):): MP: > 250 ^{o}C; Yield: 0.39 gr (87%); IR (KBr): 3465, 3325, 3099 (-NH), 1677 (-C=O), 1475, 1350 cm^{-1} (-NO_2, srteching) ; ^{1}H NMR (DMSO-d_6) δ 6.88-8.53 (m, 12H, 8H indolyl+4H isatin protons), 10.03 (s, 1H, -NH, D_2O exch.), 11.32(s, 2H, -NH, D_2O exch.); m/z: [M$^{\cdot+}$+1]: 454.

3g (R= H, R^1= Br): MP: 240-242 ^{o}C (Lit [2d] MP: 242-243 ^{o}C); Yield: 0.38 gr (90%); IR (KBr): 3422(-NH), 1715 (-C=O) ; ^{1}H NMR (DMSO-d_6) δ 6.81-8.53 (m, 12H, 8H indolyl+4H isatin protons), 10.02 (s, 1H, -NH, D_2O exch.), 11.30(s, 2H, -NH, D_2O exch.); m/z: [M$^{\cdot+}$+1]: 522.

3h (R= H, R^1= OCH_3): MP: 240-242 ^{o}C (Lit [2d] MP: 242-243 ^{o}C); Yield: 0.37 gr (89%); IR (KBr): 3382(-NH), 1688 (-C=O), 1270 cm^{-1} (C-O) ; ^{1}H NMR (DMSO-d_6) δ 3.52 (s, 6H, OCH_3), 6.64-8.23 (m, 12H, 8H indolyl+4H isatin protons), 10.43 (s, 1H, -NH, D_2O exch.), 11.52(s, 2H, -NH, D_2O exch.); m/z: [M$^{\cdot+}$+1]: 424.

5a (R= H): MP: > 250 ^{o}C; Yield: 0.31 gr (85%); IR (KBr): 3430, 3355, 3096 (-NH), 1710 cm^{-1} (-C=O); ^{1}H NMR (DMSO-d_6) δ 6.87-8.15 (m, 15H, 11H azaindolyl+4H isatin protons), 10.72 (s, 1H, -NH, D_2O exch.), 11.51(s, 2H, -NH, D_2O exch.); m/z: [M$^{\cdot+}$+1]: 366.
5b (R= F): MP: > 250 ^{o}C; Yield: 0.33 gr (88%); IR (KBr): 3395, 3322, 3107 (-NH), 1720 cm^{-1} (-C=O); ^{1}H NMR (DMSO-d_6) δ 6.88-7.24 (m, 14H, 11H azaindolyl+3H isatin protons), 10.05 (s, 1H, -NH, D_2O exch.), 11.43(s, 2H, -NH, D_2O exch.); m/z: [M$^{\cdot+}$+1]: 384
5c (R= Cl): MP: > 250 ^{o}C; Yield: 0.34 gr (86%); IR (KBr): 3385, 3342, 3113 (-NH), 1712 cm^{-1} (-C=O); ^{1}H NMR (DMSO-d_6) δ 6.90-8.18 (m, 14H, 11H azaindolyl+3H isatin protons), 10.87 (s, 1H, -NH, D_2O exch.), 11.57(s, 2H, -NH, D_2O exch.); m/z: [M$^{\cdot+}$+1]: 400.
5d (R= Br) : MP: > 250 ^{o}C; Yield: 0.39 gr (89%); IR (KBr): 3409, 3328, 3123 (-NH), 1698 cm^{-1} (-C=O); ^{1}H NMR (DMSO-d_6) δ 6.89-8.24 (m, 14H, 11H azaindolyl+3H isatin protons), 10.72 (s, 1H, -NH, D_2O exch.), 11.28(s, 2H, -NH, D_2O exch.); m/z: [M$^{\cdot+}$+1]: 444.
5e (R= I) : MP: > 250 ^{o}C; Yield: 0.44 gr (90%); IR (KBr): 3418, 3323, 3108 (-NH), 1689 cm^{-1} (-C=O); ^{1}H NMR (DMSO-d_6) δ 6.43-8.82 (m, 14H, 11H azaindolyl+3H isatin protons), 10.26 (s, 1H, -NH, D_2O exch.), 11.47(s, 2H, -NH, D_2O exch.); m/z: [M$^{\cdot+}$+1]: 492.
7a (R= H): MP: 220-222 ^{o}C (Lit[2d] MP. 222-224 ^{o}C); Yield: 0.23 gr (90%); IR (KBr): 3458, 3329, 3105 (-NH), 1705 cm^{-1}(-C=O). ^{1}H NMR (DMSO-d6) δ 5.88-7.58 (m, 10H, 6H pyrrole + 4H isatin protons), 9.70 (br s, 2 H, NH), 10.21 (s, 1 H, NH); m/z: [M$^{\cdot+}$+1]: 264.
7b (R= F): MP: > 250^{o}C; Yield: 0.25 gr (88%); IR (KBr): 3428, 3324, 3125 (-NH), 1699 cm^{-1}(-C=O). ^{1}H NMR (DMSO-d6) δ 6.12-7.89 (m, 9H, 6H pyrrole + 3H isatin protons), 9.72 (br s, 2 H, NH), 10.47 (s, 1 H, NH); m/z: [M$^{\cdot+}$+1]: 282..
7c (R= Cl): MP: 218-220 ^{o}C; Yield: 0.26 gr (89%); IR (KBr): 3418, 3317, 3098 (-NH), 1710 cm^{-1}(-C=O). ^{1}H NMR (DMSO-d6) δ 5.97-8.12 (m, 9H, 6H pyrrole + 3H isatin protons), 9.52 (br s, 2 H, NH), 10.03 (s, 1 H, NH); m/z: [M$^{\cdot+}$+1]: 298.

Results & discussion

[Bmim]OH was prepared according to the reported literature method[VIII]. To the generated yellowish oily ionic liquid were added one equivalent of isatin **1a** and 2 equiv. of indole **2a** (**Scheme 1**) and the mixture heated at 100 ^{o}C for 1 hr**,** to afford 3,3'-di(indolyl)oxindole **3a** in 85% yield on processing the reaction mixture. The same reaction was attempted out at room temperature and even after stirring for 10 hr, there was no product formation as observed by TLC. This shows that [Bmim]OH acts as an effective medium & catalyst at 100 ^{O}C for this reaction.

However, if the reaction between **1a** and **2a** was carried out in ethanol/ethanolic KOH at RT and refluxing condition, there was no product formation as observed by TLC. This indicates that [Bmim]OH acts as a task-specific ionic liquid for the synthesis of **3**. The structures of the newly synthesized compounds are supported by the spectral data.

The catalyst/reaction medium plays a vital role in determining the success of the reaction in terms of rate and yields. Various ionic liquids such as [bmim]Br, [bmim]BF_4 and [bmim]$AlCl_4$, bmim]$AlCl_4$ and [bmim]SbF_6 were screened apart from [bmim]OH, for the synthesis of bisindolyls . Among all these ionic liquids [Bmim]OH proved to be most effective as far as completion of reaction in short time & yields are concerned (**Table 1**). As shown in **Chart 1**, the ionic liquid [Bmim]OH could be recycled four times without considerable loss of activity. In order to demonstrate the scope of this reaction, series of various halo substituted isatins and substituted indoles were subjected to this reaction.

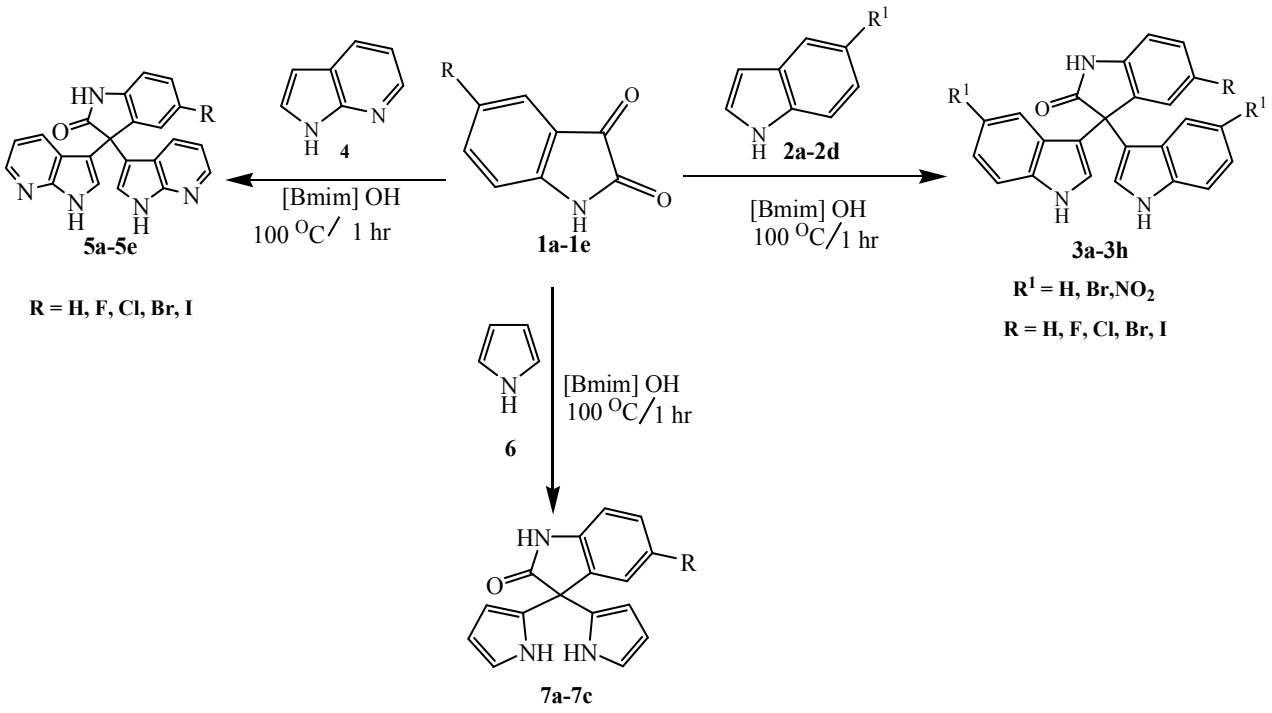
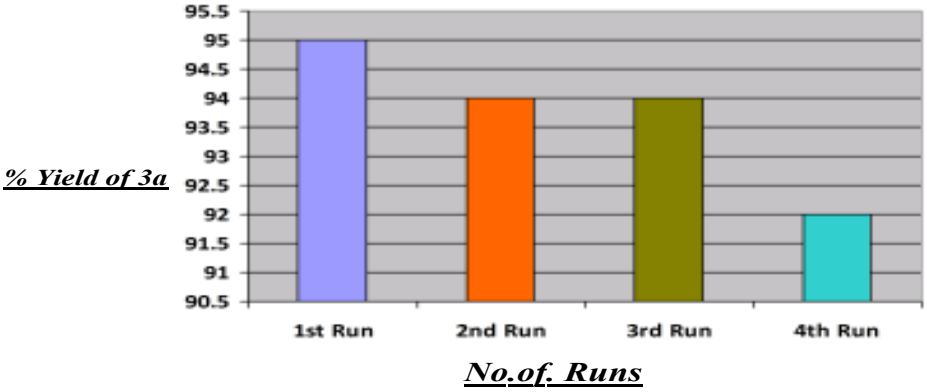


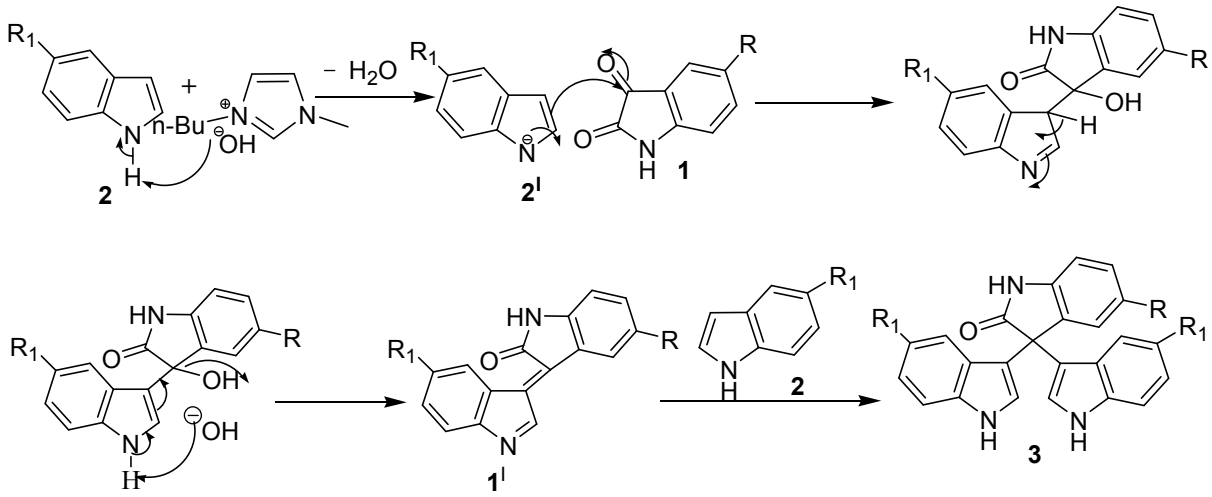
Table 1- Ionic Liquids screened for the synthesis of **3a** from **1a** & **2a**

Entry	**Ionic Liquid*** **used**	**Time (hr) of reaction**	**Temp (^{0}C)**	**Yield(%)** ** **of product 3a**
1	[bmim]Br	2	100	32
2	[bmim]BF_4	1.5	100	45
3	[bmim]$AlCl_4$	2.5	100	55
4	[bmim]SbF_6	3	100	48
5	**[bmim]OH**	1	100	85

*=Reaction carried out on a 1mmol scale; **=Isolated yield.

Chart 1: recycling of [Bmim]OH for the synthesis of **3a** from **1a** & **2a**





Scheme 2- Mechanism

Based on the above results, a mechanism (**Scheme 2**) is proposed to explain the formation of **3** from **2**. Initially, hydroxide ion of ionic liquid abstracts a proton from the indole to form the intermediate indolyl anion **2^{I}** , which further attacks carbonyl group of isatin to afford the hydroxy intermediate **1^{I}** .Reaction of another mole of indole with **1^{I}** results in the formation of **3**.

The above reaction of **1** with **2** has been extended to azaindole **4** which gave bisazaindolyloxindole **5a-5e** and to pyrrole **6** which gave **7a-7c.** The structures of **5** and **7** were assigned based on spectral data.

Conclusion

In conclusion, we report a very simple and efficient method for the synthesis of 3,3'-di(indolyl)oxindoles from the reaction of isatins and indoles, in the absence of any added catalyst. As far as possible, the reactions were carried out in an environmentally friendly medium by using [Bmim]OH as a solvent system & catalyst, thereby reducing the use of organic solvents. The products were obtained in good yields and in short reaction times. A suitable mechanism is put forward for the reaction where the solvent itself promotes the reaction.

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