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Polyethylene Gylcol (PEG-400) as an efficient and Recyclable Reaction Medium for the one pot synthesis of 3, 3'-Di (indolyl) oxindoles under catalyst-Free conditions

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ABSTRACT

Polyethylene glycol (PEG) was found to be an inexpensive nontoxic and effective medium for the one-pot synthesis of 3, 3'-Di (indolyl) oxindoles under catalyst-free conditions in excellent yields. Environmental acceptability, low cost, high yields, and recyclability of the PEG are the important features of this protocol.

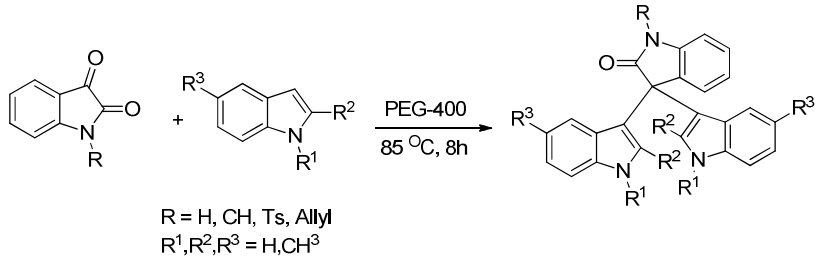
Key words: 3, 3-Di (indolyl)oxindoles, indole, isatin, Polyethylene glycol, catalyst-free conditions.

INTRODUCTION

Indole derivatives are featured widely in a wide variety of pharmacologically and biologically active compounds. [1] Oxindole derivatives are known to possess a variety of biological activity [2] The 3,3-diaryloxindoles have been shown to possess mechanism-specific antiproliferative, antibacterial, antiprotozoal, and anti-inflammatory activities.[3]

These compounds are known to exhibit potent biological and pharmaceutical activities such as anticancer, anti-HIV, antioxidant, and neuroprotective properties.[4] Indeed, a substituent at C-3 position of the oxindole plays a key role in biological activity.[5] Therefore, there is sustained interest in developing simple and efficient methods for the preparation of 3,3[1]-di(indolyl)oxindoles. Which were prepared from the reaction of isatin and indoles using a broad range of acidic catalysts such as protic acid,[6] ceric ammoniumnitrate (CAN)=ultrasound,[7] KAl(SO4)2[,8]silica sulfuricacid,[9]and Bi(OTf)3.[10]

Recently, water used as a solvent has also been used to enhance the reaction rates.[11] In recent years, the use of alternative solvents such as ionic liquids, polyethylene glycol, and super critical fluids has gained importance as green reaction media in view of environmental perception. [12, 13] though water is a safe alternative, it is not always possible to use water as a solvent due to hydrophobic nature of the reactants and the sensitivity of many catalysts to aqueous conditions. [14] In this context, PEG has become an alternative reaction media to perform organic synthesis due to its inherent advantages over toxic solvents. Furthermore, PEG is inexpensive, easy to handle, thermally stable, non-toxic, and recyclable. To the best of our knowledge, there are no reports for the synthesis of 3,3[1]-di(indolyl)oxindoles using PEG-400 as a reaction medium under catalyst-free conditions. We, herein, report a simple and efficient approach for the synthesis of 3,3[1]-di(indolyl)oxindoles under catalyst-free conditions using PEG-400 as an eco-friendly and recyclable medium **(Scheme 1).**



Scheme. Synthesis of di(indolyl)oxindoles

MATERIALS AND METHODS

All the chemicals employed in this study were procured from Sigma Aldrich and Alfaesear. In present study, all the synthetic reactions were monitored by TLC and synthesized compounds were confirmed by various spectroscopic methods. The IR spectra were recorded using KBr pellets on a Perkin Elmer IR spectrophotometer.1H NMR spectra were recorded on Brucker 300 MHz Avance NMR spectrophotometer using CdCl3 as solvent and TMS as internal standard (chemical shifts in d ppm). The mass spectra were recorded on Agilent 6300 series ion trap

The characteristic data of compounds are given below.

***(Compound 1, Table 1): 1H, 1 H-[3', 3', 3''-terindol]-2(1H)-one*:**Yield: 325 mg (90 %)IR (KBr): ν_{max}743, 1099, 1467, 1617, 1690, 3056, 3123, 3399, (NH), 3440 (NH) cmK1^{1}H NMR ($CDCl_3$, 400MHz, TMS): δ d 6.93–6.99 (m, 6H), 7.12–7.24 (m,3H), 7.34–7.40 (m, 5H), 7.74 (br, s, 1H, NH), 8.10 (br, s, 2H,NH);^{13}C NMR ($CDCl_3$, 100 MHz, TMS): δ 163.8, 161.9, 158.6, 155.9, 137.1, 132.9, 129.8, 129.8, 121.8, 120.8, 116.1, 115.9, 112.3, 111.7, 44.4, 39.3, 31.9, 29.6, 29.3, 28.6, 24.5, 22.6.Mass (ESI). : *m/z* 363 $[M+H]^+$

***(Compound 2, Table 1): 2,2''-dimethyl- 1H, 1''-[3,3',3''-terindol]-2'(1'H)-one*:** Yield: 305mg (80 %)IR (KBr): ν_{max}n1209, 1243, 1455, 1616, 1693, 2878, 2939, 3057, 3319(NH) cmK1;^{1}H NMR ($CDCl_3$, 400MHz, TMS): δ d d 3.71 (s, 6H,CH_3), 6.86 (s, 2H), 6.93–7.42 (m, 12H), 7.81 (br, s, 1H,NH);^{13}C NMR ($CDCl_3$, 100 MHz, TMS): δ 164.8, 162.9, 159.6, 155.9, 137.1, 132.9, 129.8, 129.8, 121.8, 120.8, 116.1, 115.9, 112.3, 111.7, 44.4, 39.3, 31.9, 30.6, 29.3, 28.6, 25.5, 23.6.Mass (ESI). : *m/z* 390 $[M+H]^+$

***(Compound 3, Table 1):*5,5''-dimethyl- 1H, 1''H-[3,3',3''-terindol]-2'(1'H)-one:** Yield: 298 mg (80 %%)IR (KBr): ν_{max}n 751, 1107, 1235,1466, 1614, 1712, 2853, 2914, 3386 (NH), 3413 (NH) cmK1;^{1}H NMR ($CDCl_3$, 400MHz, TMS): δ d d 2.40 (s, 6H, CH_3), 6.78 (d,2H, JZ7.6 Hz), 6.93–7.00 (m, 5H), 7.14–7.40 (m, 5H), 7.54(br, s, 1H, NH), 7.94 (br, s, 2H, NH);^{13}C NMR ($CDCl_3$, 100 MHz, TMS) : δ 9.2, 22.1, 54.2, 109.0, 110.0, 111.4, 111.6, 113.6,118.8, 119.5, 121.6, 122.0, 123.3, 124.9, 126.1, 126.6,128.9, 130.0, 130.4, 131.2, 133.4, 1 35.1, 135.9, 140.4, 178.4Mass (ESI). : *m/z* 390 $[M+H]^+$

***(Compound 4, Table 1):*5'-chloro-1H,1''H-[3,3':3',3''-terindol]-2'(1'H)-one:** Yield: 315 mg (85 %%)IR (KBr): ν_{max}n 509, 630, 761,827, 991, 1030, 1479, 1649, 2126, 2257 (NH), 3433(NH) cmK1; **^{1}H NMR** (400 MHz, DMSO) δ = 11.00 (1H, s), 10.99 (1H, s), 10.74 (1H, s), 7.38 (2H, d, *J* = 8 Hz), 7.28-7.19 (4H, m), 7.05-7.01 (3H, m), 6.90 (2H, d, *J* = 2.4 Hz), 6.85-6.81 (2H, m); **^{13}C NMR** (100 MHz, DMSO) δ = 178.40, 140.22, 136.92, 136.54, 127.70, 125.48, 124.63, 124.34, 120.99, 120.52, 118.35, 113.50, 111.66, 111.04, 52.83; NHMass (ESI).: *m/z* 396 $[M+H]^+$

***(Compound 5, Table 1):*5,5''-dibromo-1*H*,1''*H*-[3,3',3',3''-terindol]-2'(1'*H*)-one:** Yield: 292 mg (65 %%)IR (KBr):ν_{max}n n 747, 1101, 1343, 1470, 1089, 1455, 1487, 1617, 1699, 3054, 3410 (NH) cmK1;^{1}H NMR ($CDCl_3$, 400MHz, TMS) : δ d d 2.46 (s, 6H, CH_3), 6.85–7.00 (m, 8H), 7.18–7.24 (m, 3H), 7.40 (d, 1H, JZ7.2 Hz),7.73 (br, s, 1H, NH), 8.00 (br, s, 2H, NH);Mass (ESI). : *m/z* 517 $[M+H]^+$

***(Compound 6, Table 1):*1,1',1'',5,5''-pentamethyl-1H,1''H-[3,3':3',3''-terindol]-2'(1'H)-one:** Yield: 335 mg (85 %%)IR (KBr): ν_{max}n 739, 1090, 1250,1260, 1470, 1620, 1709, 3346 (NH) cmK1;^{1}H NMR ($CDCl_3$, 400MHz, TMS): δ d 7.02–7.09 (m, 2H), 7.20–7.32(m, 4H), 7.57 (d, 2H, JZ8.4 Hz), 7.96 (d, 2H, JZ8.4 Hz),8.23 (s, 2H), 10.96 (br, s, 1H, NH), 11.81 (br, s, 2H, NH)Mass (ESI).: *m/z* 432 $[M+H]^+$

***(Compound7,Table1):*5,5''-dimethoxy-1H,1''H-[3,3':3',3''-terindol]-2'(1'H)-ne:** Yield:295 mg (85 %%)IR (KBr): ν_{max}n 641,761, 832, 997, 1024, 1210, 1457, 1638, 2126 (NH), 3413(NH) cmK1; **^{1}H NMR** (300 MHz, DMSO) δ = 10.785 (2H, s), 10.58 (1H, s), 7.25-7.18 (4H, m), 7.00-6.84 (4H, m), 6.71-6.67 (4H, m), 3.51 (6H, s); **^{13}C NMR** (75 MHz, DMSO) δ = 178.73, 152.38, 141.41, 134.51, 132.15, 127.82, 126.08, 125.13, 124.95, 121.47, 113.59, 112.04, 110.39, 109.40, 103.27, 55.08, 52.47;; Mass (ESI). : *m/z 423* $[M+H]^+$

***(Compound 8, Table 1):*1',2,2''-trimethyl-1H,1''H-[3,3':3',3''-terindol]-2'(1'H)-one:**Yield: 315 mg (75 %%)IR (KBr): ν_{max}n 746, 1087, 1469, 1606, 1722, 2924,3049 cmK1;^{1}H NMR($CDCl_3$,400MHz,TMS):δdd3.35(s, 3H,CH_3), 3.70 (s, 6H, CH_3), 6.84 (d, 2H, JZ8.0 Hz), 6.91–7.18(m, 7H), 7.26–7.46 (m,5H);Mass(ES: *m/z* 404 $[M+H]^+$

***(Compound 9, Table 1):*5,5''-dinitro-1H,1''H-[3,3':3',3''-terindol]-2'(1'H)-one:** Yield: 310 mg (65 %%)IR (KBr): ν_{max}n 772, 832, 991, 1024, 1331, 1368, 2263 (NH), 3369 (NH) cmK1; **^{1}H NMR** (300 MHz, DMSO) δ = 11.71 (2H, s), 10.87 (1H, s), 8.13 (2H, d, *J* = 2.1 Hz), 7.88-7.84 (2H, m), 7.47 (2H, d, *J* = 9.0 Hz), 7.21-6.89 (6H, m); **^{13}C NMR** (75 MHz, DMSO) δ = 177.96, 141.17, 140.20, 132.90, 128.64, 128.25, 124.89, 124.57, 122.12, 117.45, 116.68, 112.45, 110.13, 52.04;Mass (ESI).: *m/z* 453 $[M+H]^+$

***(Compound 10, Table 1):*1'-tosyl-1H,1''H-[3,3':3',3''-terindol]-2'(1'H)-one:** Yield: 300 mg (85 %%)IR (KBr): ν_{max}n 734,1135, 1429, 1612, 1704, 2934, 3054, 3104, 3351 (NH) cmK1;^{1}H NMR ($CDCl_3$, 400MHz, TMS): δ d 3.74 (s, 6H, CH_3), 6.92(s, 1H), 6.96–7.32 (m, 10H), 7.47 (d, 2H, JZ8.0 Hz), 7.61(br,s,1H,NH);Mass(ESI).: *m/z* 516 $[M+H]^+$

***(Compound 11, Table 1):*5,5''-dibromo-2,2''-dimethyl-1'-tosyl-1H,1''H-[3,3':3',3''-terindol]-2'(1'H)-one.:**Yield: 280 mg (70 %%)IR (KBr): ν_{max}n 743, 1099, 1467, 1617, 1690, 3056, 3123, 3399 (NH),3440 (NH) cmK1^{1}H NMR ($CDCl_3$, 400MHz, TMS): δ 1.99(s, 3H), 6.77–6.86 (m, 4H), 6.90–7.03 (m, 3H), 7.06 (s, 1H),7.17–7.25 (m, 4H), 7.35 (d, 1H, JZ8.4 Hz), 10.60 (s, 1H),10.83 (br, s, 1H, NH), 10.94 (br, s, 1H, NH);Mass (ESI).: *m/z* 700 $[M+H]^+$

***(Compound 12, Table 1):*1'-allyl-1H,1''H-[3,3':3',3''-terindol]-2'(1'H)-one:** Yield: 315 mg (80 %%)IR (KBr): ν_{max} 751, 1099, 1468, 1615, 1711, 3047, 2842, 2909, 3123,3322 (NH), 3392 (NH) cmK1;^{1}H NMR ($CDCl_3$, 400MHz, TMS): δ d 2.31 (s, 3H), 6.94–7.38 (m, 13H), 7.55 (br, s, 1H, NH),7.98 (br, s, 1H, NH), 8.07 (br, s, 1H, NH); Mass (ESI).: *m/z* 402 $[M+H]^+$

RESULTS AND DISCUSSION

We have synthesized a series of compounds 3b–n by utilizing Isatin derivatives (1a–d) and indole derivative (2a–e) under similar conditions (Table 1). It is interesting to note that 5-methyl indole had the greatest reactivity, but 3-methyl indole did not react. One equivalent of isatin 1a and 2 equiv. of indole 2a in PEG-400 (5 Ml) were heated under heated at 85 ^{0}C for 8hours to afford 3, 31-di (indolyl) oxindoles in 85% yield. The structure of the compound was supported by the spectroscopic data, elemental analysis, and comparison with the sample prepared by the literature procedure.[15, 16]

General procedure: General procedure for the synthesis of substituted 3, 3^{1}-di (indolyl) oxindoles by using PEG as a reaction medium: A mixture of the isatin (1.0 mmol), indole (1.0 mmol), was taken in 5 ml of polyethylene glycol, and stirred at 85^{0}C for the appropriate time. After completion of the reaction, as monitored by TLC, the reaction mass was extracted with ethyl acetate (3 5 mL) and separated PEG. The combined organic layers were evaporated under reduced pressure, and the crude product was purified by column chromatography using silica gel (60–120 mesh) and hexane/EtOAc, 9:1). The recovered PEG was vacuum dried and reused for three cycles without significant loss of activity.

Table 1.PEG mediated synthesis 3,3[1]-di (indolyl) oxindoles derivatives via the condensation of isatins with Indoles

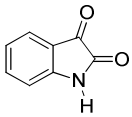
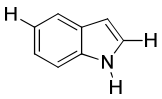
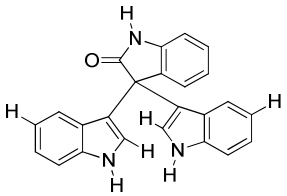
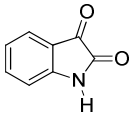
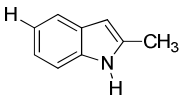
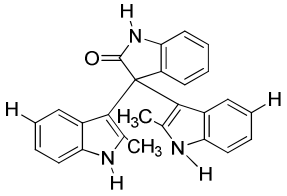
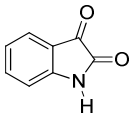
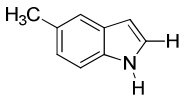
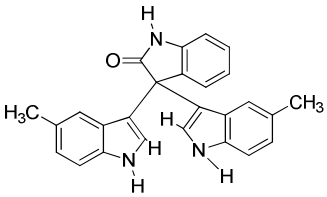
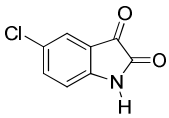
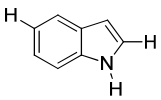
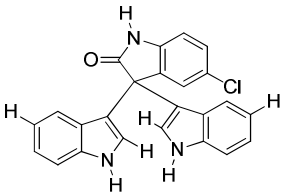
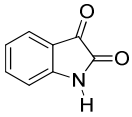
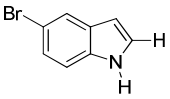
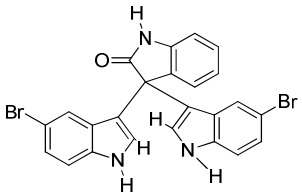
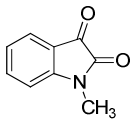
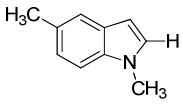
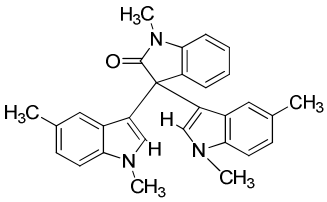
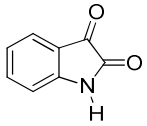
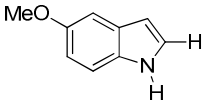
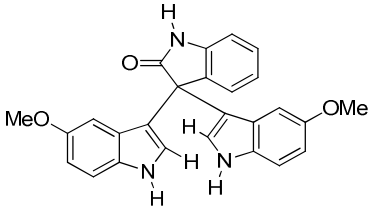
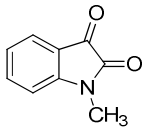
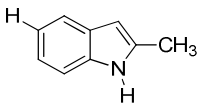
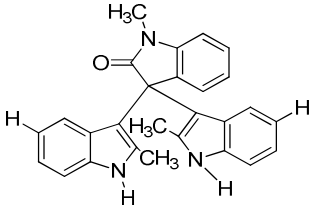
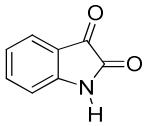
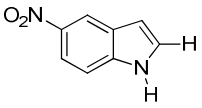
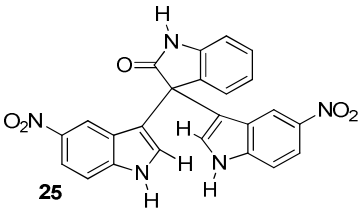
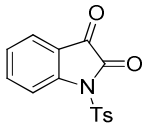
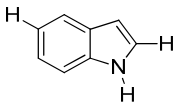
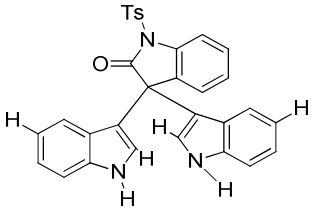
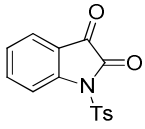
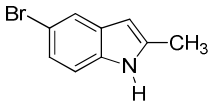
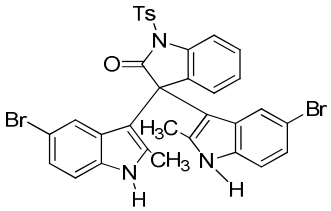
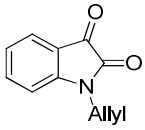
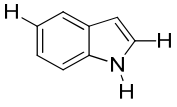
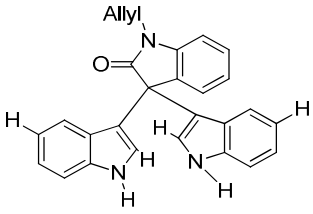
Entry	Isatin	Indoles	Product	Time(H)	Yield(%)
1				8	90
2				12	80
3				7	88
4				12	85
5				15	65
6				10	85

Table 1(Continued)

Entry	Isatin	Indoles	Product	Time(h)	Yield(%)
7				14	85
8				10	75
9			 **25**	15	65
10				12	85
11				20	70
12				14	80

[a] *Reaction conditions: isatin (1 mmol), indoles (3 mmol), PEG (5 ml), 85^{0}C.*
[b]*Isolated yield.*

In order to assess the efficiency of PEG-400, the reaction indole with isatin was also carried out in polar solvents such as DMF, DMSO, NMP, and ethylene glycol. Of these solvents, PEG-400 was found to be superior to provide the corresponding product 3l and the results are presented in Table 2.

Table 2

Entry	Solvent	Amount (mL)	Time (h)	Yield (%)
1	DMF	5	12	58
2	DMSO	5	10	60
3	NMF	5	10	57
4	Ethyleneglycol	5	10	65

CONCLUSION

We have developed an efficient approach for the synthesis of various 3,3[1]-di(indolyl) oxindoles derivatives using PEG-400 without the need of any additive or acid catalyst. The mild reaction conditions, inexpensive reaction medium, operational simplicity, and high yields are the advantages of this protocol

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