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SYNTHESIS OF SYMMETRICAL AND UNSYMMETRICAL 3,3-DI(INDOLYL)INDOLIN-2-ONES VIA FRIEDEL–CRAFTS SUBSTITUTION REACTION USING CELLULOSE SUPPORTED ACIDIC IONIC LIQUID

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ABSTRACT

A novel and highly efficient rapid protocol has been developed for the synthesis of 3,3-di(indolyl)indolin-2-ones viaFriedel–Crafts substitution reaction. C-C bond was formedby the reaction of indoles with isatins using catalytic amount of Cell-IL at room temperature in short reaction time in high yields. The generality of the method has been demonstrated by screening a series of isatin electrophiles as well as indole derivatives.

Keywords: Friedel–Crafts substitution, 3,3-di(indolyl)indolin-2-ones, C-C coupling, Heterogeneous catalyst, Solid acid catalyst

INTRODUCTION

The importance of indoles and their derivatives is well known by synthetic as well as biological chemists.[1] Since its discovery in 1866,[2] more than 80,000 papers related to indole chemistry have been published[3], Indoles have been widely used in pharmaceuticals, fragrances, agrochemicals, pigments and dyes, and material science.[4] Therefore, indole chemistry enjoys a mainstay of organic synthesis and notable interest is observed in the recent past.[3]

On the other hand, di(indolyl)indolin-2-ones are of significant importance due to their wide range of biological activities like anticancer activity[5],anticonvulsant, and antimicrobial activity[6]. 3-Arylidineindoline-2-one analogues, containing an indolinones scaffold exhibited potential HDAC inhibitory activity.[7]Indolinone hybrids also showed micromolar activity against lung cancer cells by partial depletion of intracellular Ca^{2+} stores and phosphorylation in growth inhibition assay.[8]

(Figure 1) depicts the importance of these derivatives. Inspired by these two biologically significant structures such as indole and indolinone, we envisioned that incorporation of an indole moiety into an indolinones scaffold would create a new skeleton of pharmaceutical interest.

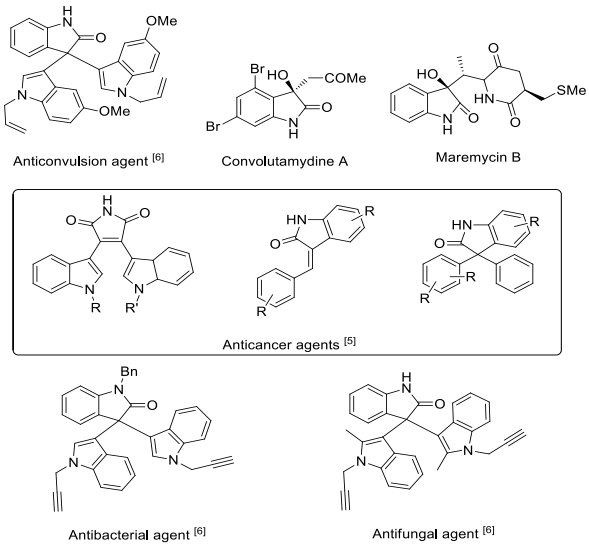


Figure 1. Some example of natural products and biologically active substances containing indole and indolinone motifs.

Friedel−Crafts reaction is one of the key reactions for carbon−carbon bond construction and has been widely used to generate important classes of building blocks.[9-11]several approaches for the formation of C-C bond via Friedel–Crafts reaction are reported in literature.[12-14] However, the reported methods often have some drawbacks like harsh reaction conditions and more catalyst loading. With the increased environmental and economic awareness, the development of greener and sustainable methods for this key transformation has emerged in recent years.[15, 16]Various synthetic methods for

the preparation of 3,3-di(indolyl)indolinones have been reported in the literature.[17-24]

Regarding scope of the reaction, almost all the reported protocols for the synthesis of 3,3-di(indolyl)indolinones, cited above, lacked the exploration of reaction in terms of yield and reaction time. Further, all of these methods suffer from at least single drawback from amongst strongly acidic or basic conditions, employing toxic reagents, costly and complex catalysts or reagents, harsh reaction conditions, tedious workup and moderate yields. Thus literature survey arose to the need to develop a protocol, which offers better results under milder reaction conditions with shorter reaction time and high yield.

In conjunction with our ongoing research, we are particularly interested in the development of biological active different heterocyclic scaffolds using green procedure,[25-36]we herein report a new simple and eco-friendly method to prepare 3,3-diindolyl oxyindolesderivatives.

EXPERIMENTAL

Materials and instrumentation

All reactions were performed using commercially available reagents. They were used without further purification.Cellulose supported ionic liquid (Cell-IL) was prepared as per our reported method.[34]The solvents used were of analytical grade. All reactions were monitored by thin-layer chromatography (TLC) on aluminium plates coated with silica gel 60 F254, 0.25 mm thickness (Merck). Detection of the components was made by exposure to iodine vapors or UV light. Melting points were taken in melting point apparatus µThermoCal10 (Analab Scientific Pvt. Ltd, India) and are uncorrected. The IR spectra were recorded in KBr on Perkin-Elmer Spectrum GX FT-IR Spectrophotometer (Perkin-Elmer, USA) and only the characteristic peaks are reported in cm^{-1}. Mass spectra were recorded on Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan) purchased under PURSE program of DST at Sardar Patel University, Vallabh Vidyanagar. The synthesized compounds were identified by ^{1}H and ^{13}C NMR spectra recorded in DMSO-d_6 as a solvent on a BrukerAvance 400 MHz spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using the residual solvent signal as an internal standard at 400 MHz and 100 MHz respectively.. Chemical shifts are reported in parts per million (ppm).

General procedure for the synthesis of 3,3-di(indolyl)indolin-2-one derivatives.

A mixture of isatins 1a-e (1 mmol), indoles 2a–d (2 mmol), and 5 mL of ethanol was stirred at room temperature in the presence of 20 mg of Cell-IL (Scheme 6.11) until the dissolution of the starting materials. The reaction progress was monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was treated with ethanol to recover the insoluble catalyst by filtration. The filtrate was then concentrated under vacuum and the desired product was obtained. The structures of the products were confirmed by ^{1}H NMR, Mass spectrometry, IR . The filtered catalyst was dried under vacuum for 3 h and was reused with fresh charge of the solvent and reactants for subsequent runs under the same reaction conditions to observe its recyclability as the efficient catalyst.

Spectral data:

***3,3-Bis(2-methyl-1H-indol-3-yl)indolin-2-one* (3a).**

Yield: 94%, mp>300 ˚C, IR (KBr, *ν*max, cm^{-1}): 3402, 3297, 1735, 1608, 1117 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.95 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 6.47 (d, J=8.4 Hz, 1H, Ar–H), 6.64 (t, 2H, Ar–H), 6.72 (d, J=8.0 Hz, 1H, Ar–H), 6.85-6.97 (m, 4H, Ar–H of indole), 7.06-7.24 (m, 4H, Ar–H of indole),10.52 (1H, s, amidic N–H), 10.84 (2H, s, N–H); ESI-MS(m/z): 392.4 (M+1).

3,3-Di(5-bromo-1H-indol-3-yl)indolin-2-one (3b).

Yield: 91%, mp>300 ˚C, IR (KBr, *ν*max, cm^{-1}):3389, 3310, 1714, 1624, 1085, 885cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ6.50 (s, 2H, Ar–H), 6.65-6.75 (m, 6H, Ar–H of indole), 6.93-6.97 (m, 4H, Ar–H), 10.91 (s, 2H, N–H), 11.28 (s, 1H, amidic N–H); ESI-MS (m/z): 522.1 (M+1).

5-Chloro-3,3-di(5-bromo-1H-indol-3-yl)indolin-2-one (3c).

Yield: 92%, mp>300 ˚C, IR (KBr, *ν*max, cm^{-1}):3411, 3289, 1721, 1602, 1118, 865cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ6.44-6.59 (m,

6H, Ar–H of indole), 6.72 (s, 2H, Ar–H), 7.07-7.16 (m, 3H, Ar–H), 10.98 (s, 2H, NH), 11.21 (s, 1H, amidic N–H); ESI-MS (m/z): 556.4 (M+1).

5-Nitro-3,3-di(5-bromo-1H-indol-3-yl)indolin-2-one (3d).

Yield: 85%, mp>300 ˚C, IR (KBr, *v*max, cm^{-1}):3424, 3294, 1733, 1619, 1109, 841cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ6.58 (s, 2H, Ar–H), 6.74-6.89 (m, 6H, Ar–H of indole), 7.13-7.27 (m, 3H, Ar–H), 11.11 (s, 2H, N–H), 11.38 (s, 1H, amidic N–H); ESI-MS (m/z): 567.3 (M+1).

5-Bromo-3,3-di(5-bromo-1H-indol-3-yl)indolin-2-one (3e).

Yield: 92%, mp>300 ˚C, IR (KBr, *v*max, cm^{-1}):3415, 3310, 1728, 1635, 1123, 877cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ6.47 (s, 2H, Ar–H), 6.54 -6.77 (m, 6H, Ar–H of indole), 6.89-7.12 (m, 3H, Ar–H), 10.90 (s, 2H, N–H), 11.18 (s, 1H, amidic N–H); ESI-MS (m/z): 601.0 (M+1).

5-Chloro-3,3-di(2-methyl-1H-indol-3-yl)indolin-2-one (3f).

Yield: 86%, mp= 292-293˚C, IR (KBr, *v*max, cm^{-1}):3389, 3326, 1698, 1614, 1142, 856cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ1.87 (s, 3H, CH3), 2.13 (s, 3H, CH3), 6.71-6.96 (m, 8H, Ar–H of indole), 7.05-7.09 (m, 2H, Ar–H), 7.62 (s, 1H, Ar–H), 11.09 (s, 2H, N–H), 11.22 (s, 1H, amidic N–H); ESI-MS (m/z): 426.8 (M+1).

5-Bromo-3,3-di(2-methyl-1H-indol-3-yl)indolin-2-one (3g).

Yield: 88%, mp= 289-291˚C, IR (KBr, *v*max, cm^{-1}):3416, 3308, 1725, 1634, 1108, 794cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ1.82 (s, 3H, CH3), 2.04 (s, 3H, CH3), 6.56-6.69 (m, 8H, Ar–H of indole), 7.11-7.16 (m, 2H, Ar–H), 7.50 (s, 1H, Ar–H),11.08 (s, 2H, N–H), 11.28 (s, 1H, amidic N–H); ESI-MS (m/z): 470.2(M+1).

***5-Nitro-3,3-di(2-methyl-1H-indol-3-yl)indolin-2-one* (3h).**

Yield: 91%, mp>300 ˚C, IR (KBr, *v*max, cm^{-1}): 3402, 3317, 1724, 1618, 1111, 795 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.96 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 6.50 (s, 1H, Ar–H), 6.65-6.75 (m, 8H, Ar–H of indole), 6.93-6.97 (m, 2H, Ar–H), 11.03 (s, 2H, N–H), 11.33 (s, 1H, amidic N–H); Anal. calcd for $C_{26}H_{20}N_4O_3$: C, 71.55; H, 4.62; N, 12.84; O, 11.00; found: C, 71.55; H, 4.57; N, 12.68; O, 11.21.

5-Nitro-3,3-di(1-methyl-indol-3-yl)indolin-2-one (3i).

Yield: 89%, mp= mp>300 ˚C, IR (KBr, *v*max, cm^{-1}):3414, 3327, 1708, 1623, 1102, 821cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ3.77 (s, 6H, 2CH3), 6.71-6.89 (m, 6H, Ar–H), 7.06 (s, 1H, Ar–H), 7.28-7.32 (m, 2H, Ar–H), 7.39-7.49 (m, 4H, Ar–H), 10.12 (s, 1H, amidic N–H); ESI-MS (m/z): 437.3(M+1).

5-Nitro-3,3-di(7-aza-1H-indol-3-yl)indolin-2-one (3j).

Yield: 84%, mp= 281-282˚C, IR (KBr, *v*max, cm^{-1}):3409, 3293, 1722, 1625, 1131, 886cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ6.44 (s, 1H, Ar–H), 6.61-6.79 (m, 6H, Ar–H of indole), 6.88-6.94 (m, 2H, Ar–H), 7.39-7.48 (m, 2H, Ar–H), 11.09 (s, 2H, N–H), 11.24 (s, 1H, amidic N–H); ESI-MS (m/z): 411.4 (M+1).

5-Chloro-3,3-di(1-methyl-indol-3-yl)indolin-2-one (3k).

Yield: 87%, mp= 292-293˚C, IR (KBr, *v*max, cm^{-1}):3407, 3313, 1717, 1608, 1121, 845cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ3.67 (s, 6H, 2CH3), 6.81-6.94 (m, 6H, Ar–H), 7.19 (s, 1H, Ar–H), 7.32-7.38 (m, 2H, Ar–H), 7.47-7.59 (m, 4H, Ar–H), 8.97 (s, 1H, amidic N–H); ESI-MS (m/z): 426.7(M+1).

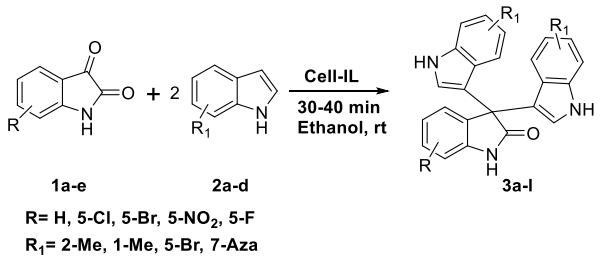
***5-Fluoro-3,3-di(1-methyl-indol-3-yl)indolin-2-one* (3l).**

Yield: 92%, mp>300 ˚C, IR (KBr, *v*max, cm^{-1}): 3421, 3292, 1741, 1618, 1090, 789 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.73 (s, 6H, $2CH_3$), 6.86-6.99 (m, 6H, Ar–H), 7.13 (s, 1H, Ar–H), 7.20-7.23 (m, 2H, Ar–H), 7.28-7.37 (m, 4H, Ar–H), 8.60 (s, 1H, amidic N–H); Anal. calcd for $C_{26}H_{20}FN_3O$: C, 76.27; H, 4.92; F, 4.64; N, 10.26; O, 3.91; found: C, 76.27; H, 4.81; F, 4.62; N, 10.36; O, 4.08.

RESULTS & DISCUSSION

Cellulose supported ionic liquid was prepared and characterized as per our reported method[34] and was used as the catalyst for synthesis of 3,3-di(indolyl)indolin-2-one derivatives. In the exploratory study of our newly proposed Friedel–Crafts process for the preparation of 3,3-di(indolyl)indolin-2-one derivatives, we carried

out first experiment by reacting simple isatin (**1a**) with 2-methyl indole (**2a**) to understand the importance of prepared catalyst to afford 3a as the product.



Scheme 1. Synthesis of 3,3 di(indolyl)indol-in-2-ones

The effectiveness of the reaction was affected by the amount of catalyst. The model reaction was attempted without any catalyst (Table 1, entry 1), which afforded the target compound 3a in very poor yield. From the performed sets of reactions, it was found that 20 mg of Cell-IL was the optimum amount of catalyst leading to 94% yield of 3a in ethanol at room temperature (Table 1, entry 5) in 30 min. Encouraged by these promising results, we then probed other catalyst for their catalytic activity towards the synthesis of 3,3-di(indolyl)indolin-2-one derivatives. Some other catalysts *viz.*, I_2, ceric ammonium nitrate (CAN), Amberlyst-15, HCl, *p*-TSA, $FeCl_3.6H_2O$, and Dowex50WX4 were found to promote the reaction with poor yield along with the impurities even after longer reaction time (Table 1, entries 9–14).It became evident that the catalysts played a vital role in the success of the reaction in terms of reaction time and yields of 3,3-di(indolyl)indolin-2-one derivatives.

Table 1. Optimization of reaction conditions[a] for the synthesis of 3a.[a]

Entry	Catalyst	Amout (mg)	Time (min) [b]	Yield (%)[c]
1	-	-	115	24
2	Cell-IL	5	85	54
3	Cell-IL	10	65	70
4	Cell-IL	15	45	81
5	Cell-IL	20	30	94
6	Cell-IL	25	40	92
7	Cell-IL	30	40	92
8	Iodine	20	75	84
9	CAN	20	85	70
10	Amberlyst-15	20	70	49
11	HCl	20	105	35
12	*p*-TSA	20	75	32
13	$FeCl_3.6H_2O$	20	70	21
14	Dowex50WX4	20	95	41

[a] Isatin (1 mmol) and 2-methylindole (2 mmol).
[b]All reactions were run in ethanol at rt till completion as indicated by TLC.
[c]Isolated yield.

Selection of an appropriate solvent for Friedel–Crafts reaction is very crucial. Among the solvents probed, ethanol was found to be the best choice for the synthesis of 3,3-di(indolyl)indolin-2-one derivatives (Table 2, entry 3).

Table 2.Solvent study on the synthesis of 3a[a].

Entry	Solvent	Time (min)[b]	Yield (%)[c]
1	-	85	56
2	Water	50	61
3	**Ethanol**	**30**	**94**
4	THF	65	35
5	Chloroform	90	59
6	DCM	80	21
7	Methanol	75	74
8	DMF	65	68

[a] Isatin (1 mmol) and 2-methylindole (2 mmol) and Cell-IL (20 mg).
[b]All reactions were run in ethanol at rt till completion as indicated by TLC.
[c] Isolated yield.

The best results were obtained with 1:2 mmol ratios of isatins and indoles in the presence of 20 mg Cell-IL at room temperature. Both the yield and reaction time for the reaction were found to be solvent and catalyst dependent. In this instance, high yield (94%) was achieved in short reaction time using Cell-IL as the catalyst (Table 1, entry 5). It was noteworthy that when I_2 was employed, 84% yield was obtained but the reaction took longer time for completion (Table 1, entry 8).

With the optimized conditions in hand, we determined the scope of the reaction with a variety of isatins (**1a-e**) and indoles (**2a-d**) (Scheme 1). Several indoles and isatin derivatives, having electron donating and electron withdrawing substituents, underwent the same reaction efficiently using Cell-IL as the catalyst. The results are listed in Table 3.

Table 3.Synthesis of 3,3-di(indolyl)indolin -2-one derivatives employing Cell-IL as the catalyst[a].

Entry	Isatins	Indoles	Products	Time (min.)[b]	Yield (%)[c]
1	H	2-CH_3	3a	30	94
2	H	5-Br	3b	30	91
3	5-Cl	5-Br	3c	35	92
4	5-NO_2	5-Br	3d	35	85
5	5-Br	5-Br	3e	35	92
6	5-Cl	2-CH_3	3f	30	86
7	5-Br	2-CH_3	3g	35	88
8	5-NO_2	2-CH_3	3h	30	91
9	5-NO_2	1-CH_3	3i	30	89
10	5-NO_2	7-aza	3j	40	84
11	5-Cl	1-CH_3	3k	30	87
12	5-F	1-CH_3	3l	30	92

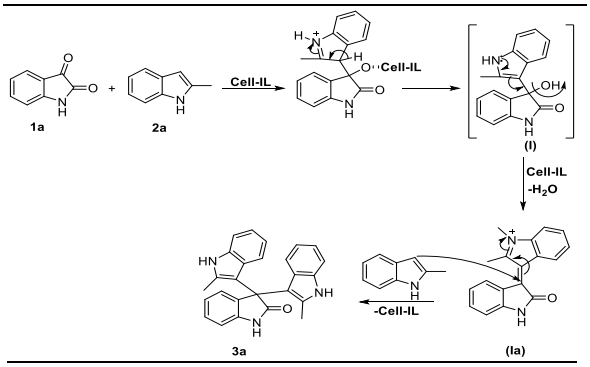
[a] Isatin (1 mmol) and 2-methylindole (2 mmol) and Cell-IL (20 mg).
[b]All reactions were run in ethanol at rt till completion as indicated by TLC.
[c] Isolated yield.

However, when 3-methyl indole was used, no reaction occured under the same conditions even after long reaction time.The yield was observed to be relatively low when 7-aza indole**2d** was used (**3j**), which may be due to the low reactivity of the aza group.

Plausible reaction mechanism:

A plausible mechanistic elucidation to explain the formation of the observed 3,3-di(indolyl)indolin-2-ones might reasonably assume a Friedel−Crafts reaction path that implies an initial activation of carbonyl group of isatin by Cell-IL. After that nucleophilic addition of the indole onto the ketonic carbonyl group of isatin to yield the corresponding 3-(indol-3-yl)-3-hydroxyindolin-2-one (**I**). Instant dehydration of this adduct gives the intermediate (**Ia**), which subsequently undergoes 1,4-nucleophilic addition of the second indole molecule to provide the final product 3,3-di(indol-3-yl)indolin-2-ones (Scheme 2).

Scheme 2. Plausible mechanism for the 3,3-di(indolyl)indolin-2-one.



The reaction was feasible without the need of metal catalyst for formation of C-C bond. All the prepared compounds were obtained in pure form after recrystallization from hot ethanol.From the leaching test of the catalyst, it was found that no homogeneous catalyst was incorporated in the product.

Recyclability of the catalyst

The recovery and reuse of the catalyst was also investigated. After the completion of reaction w, the mixture was diluted with hot ethanol and Cell-IL was removed by simple filtration. The recovered catalyst was reused for the next cycle of the same reaction.(Table 4) presents the results of the efficient recycling of the catalyst. It is seen that the Cell-IL had been reused for 5 times without any significant loss in its activity.

Table 4.Reusability study

No. of runs	Fresh	1	2	3	4	5
% Yield	94	94	93	92	91	91

CONCLUSIONS

We have reported synthesis of 3,3-di(indolyl)indolin-2-ones via Friedel–Crafts substitution reaction involving C-C bond formation using Cell-IL as the catalyst. Easy procedure associated with the high yield of products, recyclability of the catalyst, and short reaction times at room temperature rendered the method as highly viable compared to existing procedures. The efficient, convenient and novel method offered here could be of broad interest for synthetic chemists.

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