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Grindstone Chemistry: $ZnCl_2$ catalyzed efficient and facile one-pot three-component synthesis of *Bis*-indolylalkanes

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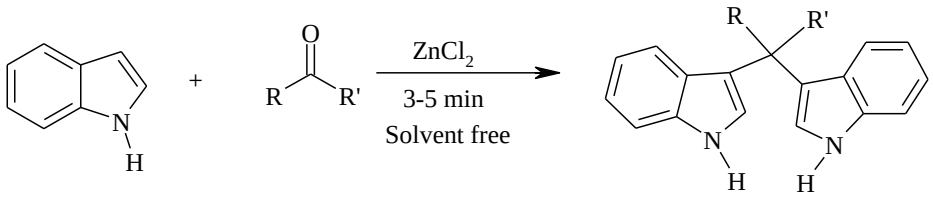
ABSTRACT

A simple, facile and an efficient one-pot three-component reaction of indole with various aldehydes and ketones in the presence of catalytic amount of Zinc chloride ($ZnCl_2$) to get *bis*-indolylalkanes in very high to excellent yield, within 3–5 min is reported. The reaction works under solvent-free condition just by *grinding* the reactants with the catalyst. There is a scope for use of 'ball mills' for preparing these pharmaceutically important compounds on a large scale.



R = Phenyl or Alkyl , R' = H or Alkyl

Key words: *Bis*-Indolylmethanes; aldehydes; ketones; indole; $ZnCl_2$; *grindstone* technique

1. Introduction

Preparation of *bis*-indolylmethane and its derivatives is important in organic synthesis because of their wide occurrence in various natural products possessing biological activity,[1] and their usefulness in the drug design.[2] *Bis*-indolylmethanes are also found to be active cruciferous substances for promoting beneficial estrogen metabolism, and for inducing apoptosis in human cancer cells.[3] Synthesis of *bis*-indolylmethanes involves the electrophilic substitution of indoles with various aldehydes or ketones in the presence of various catalysts;[4] method involving use of no-solvent and no-catalyst,[5] and the reaction in aqueous medium[6] has also been reported. Use of 5-sulphosalicyclic acid,[7] urea and choline chloride,[8] α-Chymotrypsin,[9] oxalic acid dihydrate:proline,[10] triethylborane,[11] functionalized ionic liquid[12] and use of propylsulfonic acid-anchored isocyanurate-based periodic mesoporous organosilica (PMO-ICS-Pr-SO_3H),[13] $Sc(OTf)_3$,[14] heteroaromatic isocyanurate ring functionalized MCM-41[HI-MCM-41],[15] and use of hyper-Cross-Linked polyaromatic spheres decorated with bromomethyl groups [HCP@CH_2Br][16] is also documented in the literature. However, the reported methods have one or the other disadvantages such as: use of expensive catalysts, low yields of the products, some are substrate selective reactions and some reactions involve use of complex catalysts, use hazardous solvents and require drastic conditions.

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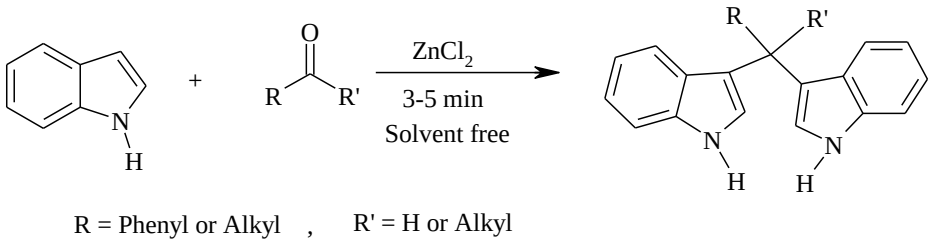
In the last decade, solvent-free organic reactions have captured great interest because of their advantages such as: high efficiency, selectivity, easy separation of products, mild reaction conditions, reduction in waste, and benefit to industry as well as the environment.[17] Further, in addition to being solvent-free if performed 'mechanochemically' the reactions are found to be more advantageous as it lowers energy and overall cost. Immediate homogenization of the reaction mixture takes place and the resulting product can be removed without use of solvents by simple filtration; and thereby reduces the complexity of the reaction.[18] Taking into account all these factors, we decided to synthesize a series of *bis*-indolylmethanes mechanochemically by *grinding* the reactants and the catalyst under solvent-free condition, and the present method matches the *Green Chemistry* protocols. On the other hand, $ZnCl_2$ is used as Lewis acid catalyst in a wide variety of reactions in organic synthesis.[19] The biggest advantages of $ZnCl_2$ are: its low cost, easy to handle nature, and is a broad spectrum Lewis acid catalyst.

In continuation with our work on the development of novel methods and novel catalysts for the synthesis of bioactive molecules,[20] in this article, we are reporting the use of catalytic amounts of $ZnCl_2$ for the synthesis of *bis*-indolylmethanes using a solvent-free *grindstone* technique by treating two molecules of indole with a molecule of various aldehydes and ketones as shown in the **Scheme-1**.



R = Phenyl or Alkyl , R' = H or Alkyl

Scheme-1: Synthesis of *bis*-indolylmethanes by *grindstone* method

2. Results and Discussion

Earlier from our laboratory, we have reported the use of *p*-TSA for the synthesis of *bis*-indolylmethanes under *grindstone* method,[21] we have now found that, the present method is equally efficient, facile and involves use of an environmentally benign catalyst $ZnCl_2$. The yields are very high and the reactions go to completion in a very short duration (3–5 min) under solvent-free condition just by *grinding* the reactants in a mortar with a pestle.

Initially, a systematic study was carried out for the evaluation of catalytic activity of $ZnCl_2$ for the reaction of indole with benzaldehyde under various conditions, and the results are presented in the **Table 1**. The reaction was slow in the absence of the catalyst (entry 1) and poor results were obtained in the presence of solvents (entries 2–9). Next, we optimized the quantity of catalyst by carrying out reactions at 25 °C under solvent-free condition (entries 10–13). The best result was obtained with 1:2:0.5 molar ratios of benzaldehyde, indole and $ZnCl_2$ under solvent-free condition (entry l2).

Table 1: Reaction of indole with benzaldehyde under various conditions

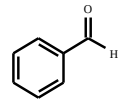
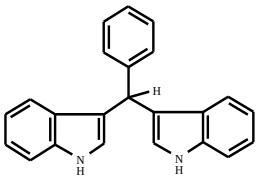
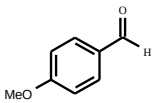
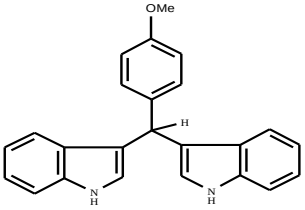
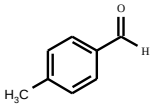
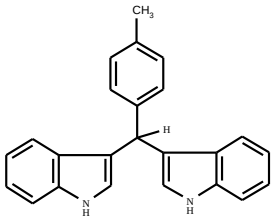
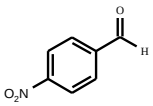
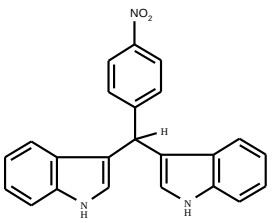
Entry	Solvent	$ZnCl_2$ (mol)	Time (min)	Yield (%)[a]
1.	Neat	--	45	Trace
2.	MeOH	1	10	57
3.	EtOH	1	10	72
4.	CH_2Cl_2	1	10	73
5.	CH_3CN	1	10	80
6.	$CHCl_3$	1	10	78

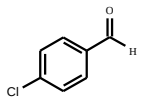
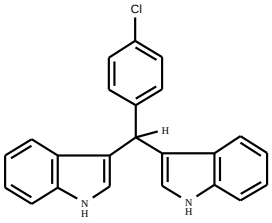
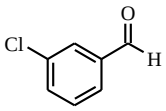
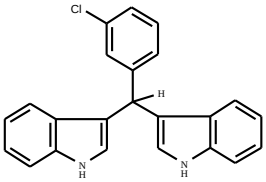
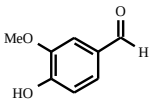
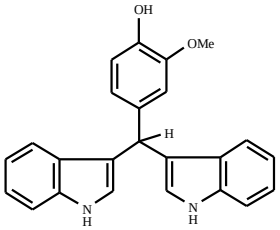
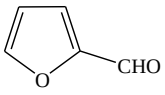
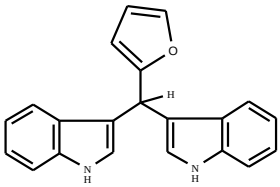
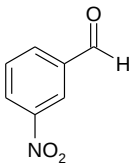
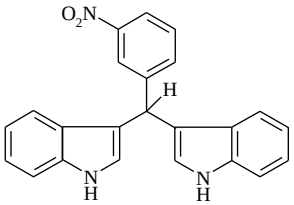
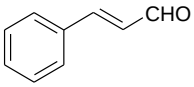
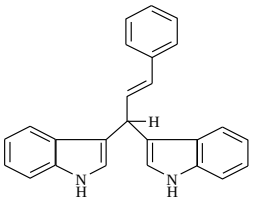
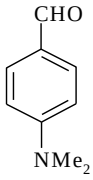
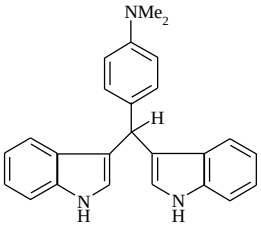
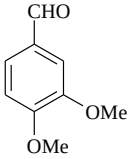
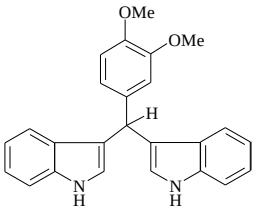
7.	THF	1	10	71
8.	DMF	1	10	67
9.	EtOAc	1	10	77
10.	Neat	2	10	82
11.	Neat	1	10	84
12.	**Neat**	**0.5**	**5**	**91**[b]
13.	Neat	0.25	10	82

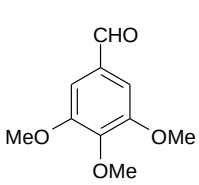
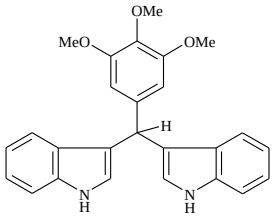
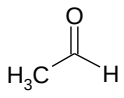
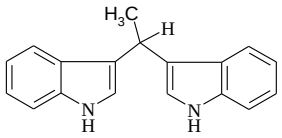
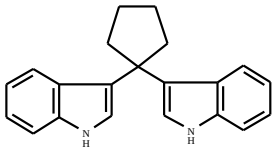
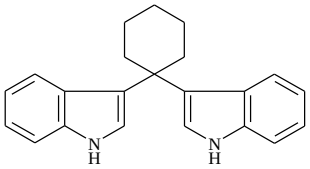
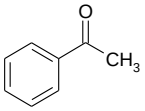
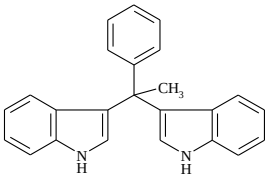
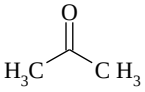
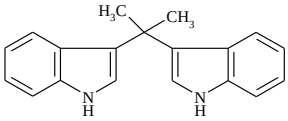
[a] Isolated yield after purification, [b] Ideal condition to get best results.

To explore the scope of this reaction and to generalize the procedure, we carried out the reaction of a series of aldehydes and ketones with indole and the results are presented in the **Table 2**. It is evident from **Table 2** that, the method works well with a wide variety of substrates. Ball mills may find application in future for scaling-up of these solid-phase reactions in chemical industries.[22]

Table 2: $ZnCl_2$ catalyzed synthesis of *bis*-indolylmethanes from aldehydes and ketones using *Grindstone* technique

Entry	Aldehyde (**2**)	Product[a] (**3**)	Time (min)	Yield[b] (%)	Melting point (°C)[c] Found	Reported
a			5	91	151	150–152
b			4	92	186	187–189
c			5	91	96	94–96
d			5	94	219	220–222

e			4	96	77-79	76–77
f			5	95	74	74
g			5	81	125	126–127
h			4	91	318	322
i			5	92	219	221–223
j			5	93	97	98–99
k			5	90	226	226
l			4	91	197-199	198–200

m			5	93	234-238[d]	--
n			5	90	147	148–150
o			5	90	73	72–74
p			4	92	119	118–120
q			5	93	191	190–192
r			5	88	64	64–66

[a] All the products are known and are characterized by either spectral analysis or by comparison with samples prepared by known methods.
[b] Isolated yields. [c] Melting points of compounds are consistent with the reported values.
[d] Novel compound.

$ZnCl_2$ catalyzed synthesis of bis(indolyl)alkanes is expected to proceed through any other Lewis acid catalyzed electrophilic substitution reaction between two molecules of indole with a molecule of aromatic or aliphatic aldehyde or a ketone.[23]

3. Experimental

All aryl aldehydes, ketones and indole were commercial products and were used without further purification. All liquid reagents and substrates were distilled before use. Yield refers to isolated product yield after chromatographic purification. Melting points were measured on a Büchi B-540 apparatus. FT-IR spectra were recorded using KBr pellets on a Nicolet 400D spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded and Bruker AMX (400-MHz and 100 MHz) instruments in

DMSO-d_6 and $CDCl_3$ respectively as solvents and TMS as an internal standard. LC-Mass spectral analysis was performed on an Agilent Technologies 1200 series instrument.

3.1 ***General Procedure for the preparation of bis-indolylalkanes*****:** A mixture of indole (2 mmol), aldehyde or ketone (1 mmol) and $ZnCl_2$ (0.5 mmol) were ground together in a mortar with a pestle at 25 °C for the appropriate time (**Table 2**). The progress of the reaction was monitored on TLC. After completion of the reaction, the reaction mixture was quenched with water and extracted with ethyl acetate (3 × 10 mL). The combined organic extract were dried over anhydrous Na_2SO_4 and concentrated *in vacuuo* to afford the crude compound. The resulting product was further purified by silica gel column chromatography (Merck, 100–200 mesh) using ethyl acetate/hexane (3:7) as an eluent to afford the pure *bis*-indolylalkanes. All the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, LC-Mass spectral analysis and by comparison of melting point with the samples prepared by the standard methods.

3.2 Spectral Data

Phenyl-3,3′-bis-indolylmethane (**3a**)
IR (KBr): ν 742, 1088, 398, 1603, 1621, 3098, 3425 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (s, 1H, Ar-CH), 6.72 (s, 2H), 7.02 (t, 2H, *J* = 6.7Hz), 7.12−7.20 (m, 3H), 7.25−7.30 (m, 2H), 7.34−7.40 (m, 6H), 7.90 (br, 2H, NH) ppm;
MS: m/z = 322 (M^+).

4′′-Methoxyphenyl-3,3′-bis-indolylmethane (**3b**)
IR (KBr): ν 1223, 1230, 1462, 1520, 1613, 2942, 3418 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 (s, 3H, CH_3), 5.78 (s, 1H, Ar-CH), 6.62 (s, 2H), 6.80 (d, 2H, *J* = 8.2 Hz), 7.16 (t, 2H, *J* = 7.2Hz), 7.16 (t, 2H, *J* = 7.3Hz), 7.21 (s, 2H), 7.26−7.40 (m, 4H), 7.87 (br, 2H, NH) ppm;
MS: m/z = 380 (M^+).

4′′-Methylphenyl-3,3′- bis-indolylmethane (**3c**)
IR (KBr): ν 772, 1062,1216, 1520, 1613, 2948, 3421 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H, Ar-CH_3), 5.82 (s, 1H, Ar-CH), 6.65 (s, 2H), 6.97 (t, 2H, *J* = 7.5 Hz), 7.20 (d, 2H, *J* = 7.3 Hz), 7.19−7.26 (m, 6H), 7.2 (d, 2H, *J* = 7.3 Hz), 7.91 (br, 2H, NH) ppm;
MS: m/z = 336 (M^+).

4′′-Nitrophenyl-3,3′-bis-indolylmethane (**3d**)
IR (KBr): ν 1353, 1472, 1562, 1600, 3052, 3432 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.18 (s, 1H, Ar-CH), 6.76 (s, 2H), 7.00−7.05 (m, 3H), 7.42 (d, 3H, *J* = 7.8 Hz), 7.40 (d, 2H, *J* = 7.9Hz), 7.49 (d, 2H, *J* = 8.6 Hz), 7.97 (br, 2H, NH), 8.00 (d, 2H, *J* = 8.3 Hz) ppm;
MS: m/z = 367 (M^+).

4′′-Chlorophenyl-3,3′-bis-indolylmethane (**3e**)
IR (KBr): ν 1092, 1474,1502, 3052, 3430 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.02 (s, 1H, Ar-CH), 6.67 (s, 2H), 7.12 (t, 3H, *J* = 8.5 Hz), 7.20 (t, 2H, *J* = 7.9Hz), 7.27−7.40 (m, 8H), 7.97 (br, 2H, NH) ppm;
MS: m/z = 356 (M^+).

3′′-Chlorophenyl-3,3′-bis-indolylmethane (**3f**)
IR (KBr): ν 1067, 1484,1512, 3082, 3473 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (s, 1H, Ar-CH), 6.71 (s, 2H), 7.16 (t, 3H, *J* = 8.7 Hz), 7.22 (t, 2H, *J* = 8.0 Hz), 7.32−7.43 (m, 8H), 8.00 (br, 2H, NH) ppm;
MS: m/z = 356 (M^+).

4′′-Hydroxy-3′′-methoxyphenyl-3,3′-bis-indolylmethane (**3g**)
IR (KBr): ν 752, 1397,1652, 3422, 3498 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.92 (br, 2H) 7.90 (s, 1H), 7.35−6.92 (m, 11H), 6.66 (s, 2H), 5.78 (s, 1H), 3.72 (s, 3H) ppm;
MS: m/z = 368 (M^+).

[2''-Furyl]-3,3'-bis-indolylmethane (**3h**)
IR (KBr): ν 1278, 1464,1732, 3428 cm^{-1};
^{1}H NMR (400 MHZ, $CDCl_3$): δ 6.23 (s, 1H, Ar-CH) 6.93 (s, 2H), 7.35−6.78 (m, 11H), 8.12 (br, 2H, NH) ppm;
MS: m/z = 312 (M^+).
3'',4'',5''-Trimethoxyphenyl-3,3'-bis-indolylmethane (**3m**, Novel compound)
Mp: 244–245 °C;
IR (KBr): ν 3395, 3040, 2947, 1593, 1506, 1456, 1423, 1326, 1220, 1151, 1122, 991, 784, 731 cm^{-1};
^{1}H NMR (400 MHz, DMSO-d_6) δ 3.38 (s, 3H), 3.65 (d, *J* = 12 Hz, 6H), 5.79 (s, 1H), 6.73 (s, 2H), 6.89 (t, *J* = 8.8 Hz, 4H), 7.04 (t, *J* = 7.2 Hz, 2H), 7.35 (t, *J* = 6.4 Hz, 4H), 10.82 (s, 2H) ppm;
^{13}C NMR (100MHz, $CDCl_3$) δ 55.77, 59.91, 105.83, 111.37, 118.03, 118.09, 119.03, 120.787, 123.43, 126.61, 135.65, 136.51, 140.68, 152.49 ppm;
MS: m/z = 412.2 (M^+).
1,1-Di-indolyl-cyclopentane (**3o**)
IR (KBr): ν 3482, 2978,1635,1595, 1498, 1032, 778 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78 (m, 4H) 2.52 (m, 4H), 6.80 (t, 2H, *J* = 8.2 Hz),7.02 (m, 4H), 7.23 (d, 2H, J = 8.2Hz), 7.50 (d, 2H, *J* = 8.2 Hz), 7.92 (br, 2H, NH) ppm;
MS: m/z = 300 (M^+).
1,1-Di-indolyl-cyclohexane (**3p**)
IR (KBr): ν 3472, 3035,2986,1635, 1592, 1492, 1239, 1019, 785 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82 (m, 6H) 2.57 (m, 4H), 6.83 (t, 2H, *J* = 8.2 Hz), 7.07 (m, 4H), 7.27 (d, 2H, *J* = 8.2Hz), 7.53 (d, 2H, *J* = 8.2 Hz) 7.90 (br, 2H, NH) ppm;
MS: m/z = 314 (M^+).

4. Conclusions

In conclusion, we have developed a very simple, inexpensive, efficient and green method for the synthesis of *bis*-indolylalkanes by a one-pot three-component reaction of aldehydes and ketones with indole using a simple, readily available and an environmentally benign catalyst: $ZnCl_2$. The method gives the products in very high to excellent yield within 3–5 min. The method is mild and is a solvent-free reaction which offers greater selectivity making this protocol practically and economically attractive. There is a scope for use of 'Ball-Mills' in future for the preparation of the target molecules on large scale in chemical industries.

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6. Conflict of Interest

The authors declare is no conflict of interest in publishing this work.

7. References

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