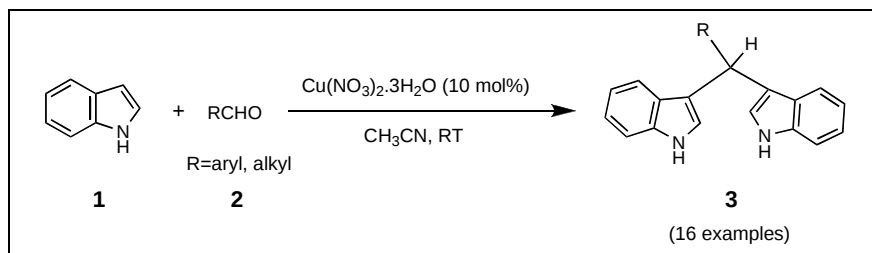


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A catalytic amount of easily available and inexpensive $\text{Cu(NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (10 mol%) enables electrophilic substitution reaction of indole with structurally divergent aldehydes in acetonitrile to afford the corresponding bis(indolyl)methanes in moderate to excellent yields (65-98%) at ambient temperature. The reaction is highly chemoselective and applicable only to aldehydes and not to ketones.

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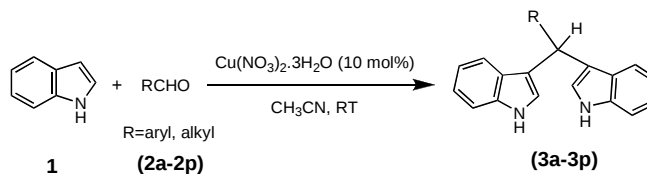
INTRODUCTION

Indole fragment is featured in a wide variety of pharmacologically and biologically active compounds [1]. For example, bisindolylalkanes and their derivatives are found in bioactive metabolites of terrestrial and marine origin (*e.g.* Vibrindole A) [2]. Interestingly, bis(indolyl)-methane is known to promote estrogen metabolism in both women and men and is expected to have an application in the prevention of breast cancer [3]. Therefore, there is a great deal of interest in the synthesis of this class of compounds [4]. Among the many methods, the synthesis of this class of compounds in the presence of Lewis acids, Bronsted acids or montmorillonite clay K-10 to promote the reaction of indoles with other aromatic or aliphatic aldehydes and ketones have been widely studied [5-11]. More recently, bis(indolyl)methanes were found to be formed in the presence of other catalysts such as metal triflates, InCl_3 , I_2 , NBS, $\text{PPh}_3 \cdot \text{HClO}_4$, $\text{AlPW}_{12}\text{O}_{40}$, silica sulfuric acid, ZrCl_4 , ionic liquids, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, La(PFO)_3 , $\text{HClO}_4 \cdot \text{SiO}_2$ and so on [12]. However many of these Lewis acids are deactivated or some times decomposed by nitrogen containing reactants. Although, these catalysts are very useful and efficient, there are still some drawbacks in most of these catalytic systems including the requirement of stoichiometric amounts of catalysts, use of expensive catalysts/media *e.g.* lanthanide triflates and ionic liquids, longer reaction times, low yields of the products, drastic conditions for the catalyst preparation and also require tedious work-up procedures [12]. Keeping in view of the tremendous pharmacological importance of bis(indolyl)methanes, cheaper and readily

available Lewis acid catalysts that secure low toxicity, efficient catalytic activity and air tolerance are still desirable.

RESULTS AND DISCUSSION

In our continued interest in the development of a highly expedient methodology for the synthesis of fine chemicals and heterocyclic compounds of biological importance [13], we report here the first example of the synthesis of bis(indolyl)methanes from the condensation of various aldehydes and indole in acetonitrile at room temperature in the presence of $\text{Cu(NO}_3)_2 \cdot 3\text{H}_2\text{O}$ as an efficient catalyst (Scheme 1).



Scheme 1

Initially, we have studied the efficacy of several metal nitrates chosen (10 mol% as standard) for the model reaction using indole **1** (2 mmol) and benzaldehyde **2a** (1 mmol) in acetonitrile (3 mL), being stirred at ambient temperature for 1 h, to afford the corresponding bis(indolyl)methane and the results are shown in Table 1. While comparing the effect of catalysts, we found that, $\text{Cu(NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (entry 7, Table 1) was more effective than other nitrates tested, in terms of isolated yields (96%). As shown in Table 1, while other nitrates such as

$\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (entry 3), $\text{La}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (entry 5), $\text{Nd}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ (entry 6) and $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (entry 11) are also equally efficient, we chose $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ as the suitable catalyst for further reactions due to its ready availability and cost effectiveness.

Table 1. Comparison of the effect of various metal nitrates for the condensation reaction of indole **1** with benzaldehyde **2a** for a period of 1 h.

Entry	Catalyst	Yield (%) ^a
1	$\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$	55
2	AgNO_3	48
3	$\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$	92
4	$\text{Rh}(\text{NO}_3)_3 \cdot 2\text{H}_2\text{O}$	81
5	$\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$	90
6	$\text{Nd}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$	94
7	$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$	96
8	$\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$	77
9	$\text{Ni}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$	52
10	$\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$	78
11	$\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$	90

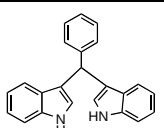
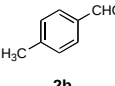
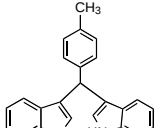
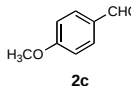
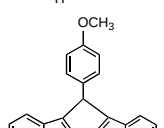
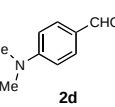
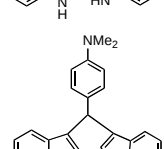
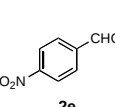
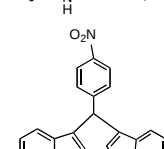
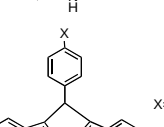
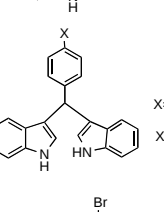
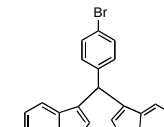
^aIsolated Yields.

Intrigued by these observations, we have then tested the efficacy of several copper salts available such as $\text{Cu}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$, $\text{Cu}(\text{I})\text{X}$ (Cl, Br, I), $\text{Cu}(\text{acac})_2$ along with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ for the model reaction (10 mol% as standard) and among the copper salts screened, $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ was found to be the best both in terms of reaction times and yields.

To examine the influence of effect of various solvents for the model reaction, we also carried out the reaction in various organic solvents such as DCM (85%), acetone (65%), CH_3CN (96%), MeOH (86%), DMSO (77%) and chloroform (82%) during the period and among the screened, acetonitrile was found to be the choice of solvent. An optimum amount of 10 mol% of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ in acetonitrile is sufficient to carry forward the reaction. Increasing or decreasing the catalyst loading, did not improve the yields {(1 mol% (0 %), 2 mol% (10-12%), 5 mol% (45%), 7.5 mol% (61%), 10 mol% (96%), 20 mol% (89%)} for the specified time. In the absence of the catalyst, the reaction did not yield any product even after stirring for 2 days.

Encouraged by these results obtained for benzaldehyde, we generalized the reaction scope for a number of other structurally divergent aromatic as well as aliphatic aldehydes and ketones to probe their behaviour under the optimized reaction parameters, *i.e.*, 10 mol% $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ in acetonitrile, and Table 2 summarizes the observations. All products were well characterized by ^1H nmr and mass spectral analysis, and compared with authentic samples. The nature of substituents on aromatic ring showed some effects on this conversion.

Table 2. $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ -catalyzed synthesis of bis(indolyl)methanes from indole and divergent aldehydes.

Entry	Aldehyde (2)	Product (3)	Time (h)	Yield (%) ^a [ref]
1	 2a		1.0	96 [12d]
2	 2b		1.0	92 [12d]
3	 2c		1.5	98 [12d]
4	 2d		6.0	88 [12]
5	 2e		5.5	82 [12d]
6	 2f X = F		2.0	90 [12]
7	 2g X = Cl		2.5	94 [12e]
8	 2h		3.0	92 [12]

^aYields refer to the isolated pure products.

In general, electron-deficient aldehydes such as nitro, *N,N*-dimethyl and so forth, required longer reaction times to produce comparable yields than those of their simple and electron-rich counterparts (entries 2-8). *p*-Hydroxy benzaldehyde (entry 9) and cinnamaldehyde (entry 10) are also tolerant and revealed good reactivities without undergoing polymerization or isomerization. Heteroaromatic aldehydes such as pyridine 2-carboxaldehyde (entry 12) and furfuraldehyde (entry 13) survived well without the formation of any side products under the present reaction conditions giving the corresponding bis(indolyl)methanes in moderate yields. Furthermore, both cyclic and acyclic aliphatic aldehydes gave the products in good yields (entries 14-16).

Table 2. Continued.

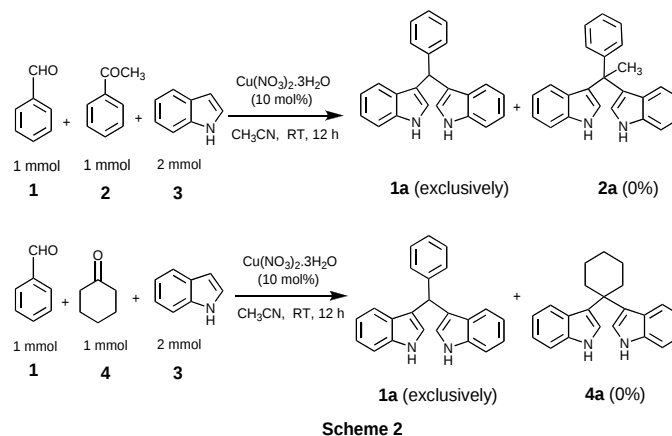
Entry	Aldehyde (2)	Product (3)	Time (h)	Yield (%) ^a [ref]
9			3.0	78 [12h]
10			2.5	83 [12n]
11			2.0	94 [12j]
12			2.5	65 [12n]
13			2.5	72 [12d]
14			3.0	76 [12o]
15			1.5	84 [12e]
16			1.0	86 [12o]

^aYields refer to the isolated pure products.

There were some limitations for the $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ catalyzed reaction. The reactions with aliphatic and aromatic ketones such as cyclohexanone and acetophenone were found to be unsuccessful. On the basis of these reactivity differences of the aldehydic and keto functionalities, few competitive experiments were conducted to study the efficacy of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ catalyzed selective synthesis of corresponding bis(indolyl)methanes (**Scheme 2**).

Reaction of benzaldehyde (1 mmol) and acetophenone (1 mmol) with indole (2 mmol) afforded the corre-

sponding benzaldehyde derived bis(indolyl)methane exclusively even after stirring for 12 h. Likewise, reaction of benzaldehyde (1 mmol) and cyclohexanone (1 mmol) with indole (2 mmol) also yielded the corresponding benzaldehyde condensed product chemoselectively. This selectivity might be useful to differentiate aldehydes from ketones through the synthesis of bis(indolyl)methanes.



The efficiency and generality of the present $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ -catalyzed protocol can be realized at a glance by comparing our results for the reaction of benzaldehyde with indole chosen as model substrate with those of some recently developed procedures (as shown in Table 3). The reactions have been compared with respect to the reaction times, mol-% of the catalyst used and the yields. As it is evident from Table 3, our protocol is comparatively better in terms of ready availability, easy handling, cost effectiveness and remarkably low toxicity, with most of the recently reported catalysts.

The reaction most probably proceeds initially activation of aldehyde by the catalyst to undergo electrophilic substitution reaction at C-3 of an indole, and after loss of water to produce azafulvenium salt. The formed azafulvenium salt then undergoes further addition with second indole molecule to afford bis(indolyl)methane derivatives as elegantly proposed by Wang *et al.*¹¹

Conclusion

In summary, we have developed a practical and new procedure for the synthesis of bis(indolyl)-methanes using $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ as catalyst. The present protocol has several advantages: readily available and inexpensive catalyst, mild reaction conditions (at room temperature), moderate to excellent yields, greater selectivity, operational and experimental simplicity, study of wide range of structurally divergent aldehydes. We believe that this $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ -catalyzed methodology will definitely be a valuable addition to the existing

Table 3. Comparison of catalytic efficiency of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ against some recently reported catalysts for the reaction of benzaldehyde with indole

Entry	Catalyst	Mol-%	Time (min/h)	Yield (%) ^a	Ref.
1	$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O} / \text{CH}_3\text{CN}$	10	1.0 h	96	-
2	$\text{LiClO}_4 / \text{CH}_3\text{CN}$	10	5.0 h	90	[12o]
3	I_2 / Neat	20	10 min	72	[12d]
4	$\text{La}(\text{PFO})_3 / \text{EtOH}$	5	0.5 h	90	[12e]
5	$\text{Dy}(\text{OTf})_3$	2	12 h	95	[11]
6	NBS/Neat	10	0.5 h	99	[12i]
7	$\text{FeCl}_3 \cdot 3\text{H}_2\text{O} / \text{IL}$	5	1.5 h	98	[12k]
8	$\text{AlPW}_{12}\text{O}_{40} / \text{CH}_3\text{CN}$	2	15 min	92	[12h]
9	$\text{In}(\text{OTf})_3 / \text{IL}$	5	15 min	90	[12m]
10	Silica Sulfuric acid/Neat	13	40 min	92	[12g]
11	$\text{ZrCl}_4 / \text{CH}_3\text{CN}$	10	30 min	96	[12j]

^aIsolated yields.

processes in the field of syntheses of bis(indolyl)-methanes.

EXPERIMENTAL

All reagents were obtained from commercial sources and used without further purification. Solvents for chromatography were distilled before use. nmr spectra were recorded on Varian FT-200 MHz (Gemini) and Bruker UX nmr FT-300 MHz (Avance) instruments, in CDCl_3 . Chemicals shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as internal standard. Electron-impact (EI) mass spectra were recorded on a VG 7070H Micromass mass spectrometer at 200 °C, 70 eV. Elemental analyses were performed by Elementar analyzer Vario EL. Melting points have been recorded on an Electrothermal melting point apparatus. The ir spectra were obtained with Perkin Elmer 240-C instrument using potassium bromide pellets/neat. Analytical TLC of all reactions was performed on Merck precoated plates (silica gel 60F-254 on glass). Column chromatography was performed using Acme silica gel (100–200 mesh).

Typical procedure for the synthesis of bis(indolyl)methane (3a). To the stirred solution of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (10 mol%) in acetonitrile (3 mL) were added successively indole (2 mmol) and benzaldehyde (1 mmol) at room temperature for the time specified in Table 1. After completion of the reaction, the crude product was extracted with diethyl ether, dried over anhydrous MgSO_4 , concentrated under reduced pressure to furnish the crude product, which was further purified by silica gel chromatography using $\text{EtOAc}/\text{Hexane}$ (1:9), to afford corresponding product as light pinkish solid (96%, **3a**). All compounds are known and gave satisfactory spectroscopic data in accordance to their proposed structures.¹²

3,3'-Bis-indolyl(phenyl)methane 3a (entry 1, Table 2): Solid, mp 125–126 °C, ir (potassium bromide): ν 3416, 1634, 1378, 737 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 5.89 (s, 1H), 6.66 (d, J = 1.8 Hz, 2H), 7.01 (t, J = 7.4 Hz, 2H), 7.17 (t, J = 7.8 Hz, 3H), 7.28–7.37 (m, 8H), 7.91 (br s, 2H, NH); ^{13}C nmr (deuteriochloroform): δ 21.5, 114.3, 118.9, 119.4, 123.0, 125.1, 127.1, 130.0, 130.1, 130.2, 133.7, 134.3, 137.1; ms (electron impact): m/z 322 (100, M^+), 245 (49), 204 (25), 122 (35), 105

(20), 77 (10); Anal Calcd. for $\text{C}_{23}\text{H}_{18}\text{N}_2$ (%): C, 85.68; H, 5.63; N, 8.69; Found: C, 85.59; H, 5.68; N, 8.54.

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