An Efficient Preparation of Bis(indole)methanes Catalyzed by Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate Salts in Aqueous Medium

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Abstract: An efficient and direct preparation of bis(indole)methanes from indole and the corresponding carbonyl compound in water catalyzed by metal salts of tetrakis[3,5bis(trifluoromethyl)phenyl]borate has been developed.

Key words: indoles, catalysis, condensation, aldehydes, aqueous reactions

Bis(indole)methanes and derivatives, a class of bioactive intermediates of terrestrial and marine origin, are important organic compounds.^{1,2} For this reason, remarkable efforts have been made to develop efficient methods for their preparation. They can be prepared by the condensation of indoles with various aldehydes or ketones in the presence of acidic catalysts. In recent years, syntheses of this class of molecules under mild conditions have been reported, with promoters such as zinc(II) chloride/acetic acid,³ ethanol,⁴ formic acid,⁵ cyclodextrin/electrolysis,⁶ zirconium(IV) chloride,⁷ sulphamic acid,⁸ copper(II) bromide,9 Amberlyst,10 potassium hydrogen sulfate,11 iodine,¹² lithium perchlorate,¹³ and ionic liquid.¹⁴ However, many of these methods still suffer from some disadvantages such as long reaction times, the use of organic solvents, and high catalyst loading. Therefore, a more efficient method for this transformation in an aqueous medium is still required. In this context, a few reports show that the preparation of bis(indole)methanes can be achieved in water.^{15–18} In these instances, the high quantity of catalyst needed for better conversion remains an issue to be improved.

In our previous work, we have found that sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate dihydrate (NaBAr^F₄·2H₂O) is able to provide a proton to initiate the polymerization of vinyl ether in organic solvent.¹⁹ This sodium salt could also assist the hydrolysis of acetals²⁰ and catalyze the Mannich reaction in aqueous solution,²¹ thus demonstrating that this salt is a good acid catalyst. On the basis of these findings, we have carried out a study on the preparation of bis(indole)methanes by the condensation of indole and aldehydes (or ketones) catalyzed by NaBAr^F₄ in aqueous medium.

As a starting point, we selected the reaction of benzaldehyde with two equivalents indole as a model to examine

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the effectiveness of various salts on this reaction (Scheme 1). It was surprising to find that bis(indol-3-yl)(phenyl)methane (1a) was efficiently obtained under extremely mild conditions when NaBAr^F₄ was used. In addition, a series of salts were also screened for this reaction, and the results are listed in Table 1.

Group I and II metal salts of tetrakis[3,5-bis(trifluoromethyl)phenyl]borate appeared to be excellent catalysts for this condensation (Table 1, entries 6–10). On the other hand, a simple salt such as sodium chloride or bromide does not show good catalytic activity (Table 1, entries 2– 4), and the activity of sodium tetraphenylborate is already slightly better than that of sodium bromide (Table 1, entries 5 and 3, respectively). From these results, we noticed that the tetrakis[3,5-bis(trifluoromethyl)phenyl]borate an-



Scheme 1

 Table 1
 Effect of Type of Salt as Catalyst on the Reaction of Indole with Benzaldehyde^a

Entry	Salt	Yield (%)
1	none	5
2	NaCl	12
3	NaBr	15
4	NaBF ₄	13
5	$NaBPh_4$	31
6	LiBAr ^F ₄	99
7	NaBAr ^F ₄	96 ^b
8	$KBAr_{4}^{F}$	86
9	$Mg(BAr^{F_4})_2$	92
10	Ca(BAr ^F ₄) ₂	89

 $[^]a$ Reaction conditions: indole (2 mmol), PhCHO (1 mmol), salt (2 μ mol), H₂O (2 mL), 30 °C, 6 h.

^b After 5 h, instead of 6 h.

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Figure 1 Plots of yield versus time for the reaction of indole with benzaldehyde catalyzed by various metal salts of tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

ion plays an important role in this catalysis. As for metal ions, there is no significant difference among them. A plot of yield versus time for various $MBAr_4^F$ in this catalysis is given in Figure 1. All metal ions catalyzed the reaction similarly at the beginning of the reaction, but slightly differently after one hour.

We also investigated the effect of solvents other than water on this reaction. As shown in Table 2, water appears to be essential for this reaction. Reactions in most of the organic solvents provided the desired product in moderate or poor yield. However, addition of water to these organic solvents readily improved the reaction yields (Table 2, entries 3 and 7). In water, the sodium salt of tetrakis[3,5bis(trifluoromethyl)phenyl]borate and organic substrates would form a colloidal dispersion during the reaction. The emulsion appeared to accelerate the reaction, which is similar to the phenomenon occurring during the Mannich reaction catalyzed by NaBArF₄ in water.²¹ Apparently, NaBAr^F₄ plays two major roles in this reaction: that of catalyst and that of surfactant. It is known that the formation of colloidal particles can speed up organic reactions, and a typical example has been illustrated by Kobayashi and coworkers for the Mannich-type reaction catalyzed by dodecylbenzenesulfonic acid.²² Since the salt dissolves in *N*,*N*-dimethylformamide or acetonitrile, this explains why the reactions in these solvents give the least satisfactory results (Table 2, entries 8 and 9).

The reactions of various carbonyl compounds with indoles were then studied under the optimized conditions, and the results are compiled in Table 3. In all instances, the reactions of either aromatic or aliphatic aldehydes with indole proceeded smoothly in high yields (Table 3, entries 1–5). The beneficial effect of NaBAr^F₄ on this condensation was also applicable to ketones as reagents, and the reaction of cyclohexanone with indole provided the corresponding bis(indole) derivative in 65% yield (Table 3, entry 6). Various substituted indoles react with aromatic aldehydes to give the desired products in excellent yields, and it appears that substituents have little effect on this catalysis. The reaction of terephthalaldehyde (1 mmol) with indole (4 mmol) also proceeded smoothly, to give 3,3',3",3"'-(1,4-phenylenedimethanetriyl)tetrakis(1H-indole) (7) in 68% yield (Table 3, entry 16).

 Table 2
 Effect of Type of Solvent on the Reaction of Indole with Benzaldehyde^a

Entry	Solvent	Yield ^b (%)		
1	H ₂ O	100		
2	MeOH	50		
3	MeOH-H ₂ O (1:1)	88		
4	CH ₂ Cl ₂	35		
5	toluene	55		
6	THF	22		
7	THF-H ₂ O (1:1)	80		
8	DMF	trace		
9	MeCN	trace		

^a Reaction conditions: indole (2 mmol), PhCHO (1 mmol), NaBAr $_{4}^{F}$ (2 µmol), solvent (2 mL), 30 °C, 6 h.

^b Yield by NMR spectroscopy.

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Table 3 Preparation of Bis(indole)methane Derivatives^a

Entry	Indolo	Carbonyl	Draduat	Time	Vialdb
Ени у	Indole	compound	Flouuet	(h)	(%)
1		PhCHO	1a	5	99
2		РМРСНО	1b	6	98
3		Me(CH ₂) ₆ CHO	1c	6	92
4		2-furylCHO	1d	8	78
5		руСНО	1e	8	71
6		cyclohexanone	1f	10	65
7		PhCHO	2a	1.5	96
8		4-O ₂ NC ₆ H ₄ CHO	2b	3	93
9		TolCHO	2c	2	95

Table 3 Preparation of Bis(indole)methane Derivatives^a (continued)

Entry	Indole	Carbonyl compound	Product	Time (h)	Yield ^b (%)
10	N Me	РМРСНО	2d	2.5	94
11	Me	PhCHO	3a	2	95
12	Me	РМРСНО	3b	3	92
13	Br	PhCHO	4	5	93
14	MeO	PhCHO	5	6	91
15		РһСНО	6	8	92
16		C ₆ H ₄ -1,4-(CHO) ₂	7	12	68

 a Reaction conditions: indole (2 mmol), carbonyl compound (1 mmol), NaBAr $^{F_4}_4$ (2 µmol), H₂O (2 mL), 30 °C. b Isolated yield.

In conclusion, this procedure offers several advantages in the preparation of bis(indole)methanes, such as mild conditions, low catalyst loading, high yields, and the use of aqueous medium; this makes it an attractive and useful methodology for organic synthesis. From the study of the anions, it is quite clear that tetrakis[3,5-bis(trifluoromethyl)phenyl]borate plays the role of surfactant in assisting the electrophilic substitution of indoles.

¹H and ¹³C NMR spectra of samples in CDCl₃ were recorded on a Bruker Avance 400 spectrometer. Chemical shifts are reported in ppm relative to TMS. Chemicals and solvents were of analytical grade and used as received unless otherwise stated. De-ionized water was used for this study. Salts of tetrakis[3,5-bis(trifluoromethyl)phenyl]borate were prepared according to a previously reported procedure.¹⁹

Bis(indol-3-yl)(phenyl)methane (1a);²³ Typical Procedure

A mixture of indole (2 mmol), benzaldehyde (1 mmol), and NaBAr^F₄ (2 μ mol) in H₂O (2 mL) was stirred at 30 °C for 5 h. The mixture was filtered through a short column (Celite, 2 g) to remove the salt. Concentration of the filtrate gave the crude product, which was either recrystallized from organic solvents or chromatographed (silica gel) to yield the pure product.

Pink solid; mp 120-123 °C.

¹H NMR (400 MHz, CDCl₃): δ = 5.83 (s, 1 H), 6.53 (s, 2 H), 6.95 (t, *J* = 8 Hz, 2 H), 7.11 (t, *J* = 8 Hz, 2 H), 7.20–7.30 (m, 5 H), 7.35 (m, 4 H), 7.89 (br, 2 H, N*H*).

Bis(indol-3-yl)(4-methoxyphenyl)methane (1b)¹⁵

Brown solid; mp187–189 °C.

¹H NMR (400 MHz, CDCl₃): δ = 3.76 (s, 3 H), 5.82 (s, 1 H), 6.63 (s, 2 H), 6.80 (d, *J* = 8.4 Hz, 2 H), 7.00 (t, *J* = 7.6 Hz, 2 H), 7.12–7.24 (m, 4 H), 7.32–7.38 (m, 4 H), 7.91 (br, 2 H, NH).

1,1-Bis(indol-3-yl)octane (1c)

Green oil.

¹H NMR (400 MHz, CDCl₃): $\delta = 0.85$ (s, 3 H), 1.23–1.43 (m, 10 H), 2.21 (dt, J = 7.2, 6.8 Hz, 2 H), 4.46 (t, J = 7.2 Hz, 1 H), 6.97 (d, J = 2 Hz, 2 H), 7.02 (t, J = 8 Hz, 2 H), 7.13 (t, J = 8 Hz, 2 H), 7.31 (d, J = 8 Hz, 2 H), 7.58 (d, J = 8 Hz, 2 H), 7.87 (br, 2 H, NH).

¹³C NMR (100 MHz, CDCl₃): δ = 14.1, 22.6, 28.3, 29.2, 29.7, 31.9, 33.9, 35.8, 111.1,118.9,119.4, 120.3, 121.4, 121.6, 127.0, 136.4.

ESI-HRMS: m/z [M + Na] calcd for C₂₄H₂₈N₂: 367.2150; found: 367.2145.

2-Furylbis(indol-3-yl)methane (1d)²⁴

Green solid; mp 318–320 °C.

¹H NMR (400 MHz, CDCl₃): δ = 5.93 (s, 1 H), 6.05 (d, *J* = 2.4 Hz, 1 H), 6.23 (dd, *J* = 2.4, 1.6 Hz, 1 H), 6.84 (s, 2 H), 7.02 (t, *J* = 8 Hz, 2 H), 7.16 (t, *J* = 8 Hz, 2 H), 7.33 (m, 3 H), 7.46 (d, *J* = 8 Hz, 2H), 7.94 (s, 2 H).

Bis(indol-3-yl)(2-pyridyl)methane (1e)²⁵

Brown solid; mp 238-240 °C.

¹H NMR (400 MHz, CDCl₃): $\delta = 6.02$ (s, 1 H), 6.63 (s, 2 H), 6.95 (t, J = 8 Hz, 2 H), 7.04 (d, J = 8 Hz, 1 H), 7.12 (t, J = 8 Hz, 2 H), 7.17 (d, J = 6.6 Hz, 1 H), 7.27 (d, J = 8 Hz, 2 H), 7.35 (d, J = 8 Hz, 2 H), 7.51–7.55 (m, 1 H), 8.40 (br, 2 H), 8.53 (d, J = 4.8 Hz, 1 H).

1,1-Bis(indol-3-yl)cyclohexane (1f)¹³ White solid; mp 117–119 °C

¹H NMR (400 MHz, CDCl₃): δ = 1.60–1.69 (m, 2 H), 1.70–1.73 (m, 4 H), 2.54 (t, *J* = 5.6 Hz, 4 H), 6.87 (s, 2 H), 7.04 (t, *J* = 8 Hz, 2 H), 7.08 (t, *J* = 8 Hz, 2 H), 7.28 (t, *J* = 8 Hz, 2 H), 7.54 (t, *J* = 8 Hz, 2 H), 7.90 (br, 2 H).

Bis(1-methylindol-3-yl)(phenyl)methane (2a)²⁶ Pink solid; mp 204–206 °C.

¹H NMR (400 MHz, CDCl₃): δ = 3.67 (s, 6 H), 5.87 (s, 1 H), 6.52 (s, 2 H), 6.98 (t, *J* = 7.6 Hz, 2 H), 7.20 (t, *J* = 7.6 Hz, 2 H), 7.25–9.29 (m, 5 H), 7.33–7.38 (m, 4 H).

Bis(1-methylindol-3-yl)(4-nitrophenyl)methane (2b)²⁷ Yellow solid; mp 215–217 °C.

¹H NMR (400 MHz, CDCl₃): δ = 3.69 (s, 6 H), 5.96 (s, 1 H), 6.52 (s, 2 H), 7.02 (t, *J* = 8 Hz, 2 H), 7.21 (t, *J* = 8 Hz, 2 H), 7.30 (m, 4 H), 7.47 (d, *J* = 8.8 Hz, 2 H), 8.11 (d, *J* = 8.8 Hz, 2 H).

Bis(1-methylindol-3-yl)(4-tolyl)methane (2c) Brown solid; mp 198–200 °C.

¹H NMR (400 MHz, CDCl₃): δ = 2.32 (s, 3 H), 3.67 (s, 6 H), 5.83 (s, 1 H), 6.52 (s, 2 H), 6.98 (t, *J* = 7.6 Hz, 2 H), 7.06 (d, *J* = 8 Hz, 2 H), 7.16–7.28 (m, 6 H), 7.37 (d, *J* = 8 Hz, 2 H).

 ^{13}C NMR (100 MHz, CDCl₃): δ = 21.2, 32.7, 39.7, 108.9, 118.3, 118.4, 119.9, 121.2, 127.3, 128, 128.4, 128.7, 135.2, 137.2, 141.2.

ESI-HRMS: m/z [M + Na] calcd for C₂₆H₂₄N₂: 387.1837; found: 387.1877.

(4-Methoxyphenyl)bis(1-methylindol-3-yl)methane (2d)²⁸ Brown solid; mp 220–222 °C.

¹H NMR (400 MHz, $CDCl_3$): $\delta = 3.66$ (s, 6 H), 3.77(s, 3 H), 5.81 (s, 1 H), 6.50 (s, 2 H), 6.80 (d, J = 8.8 Hz, 2 H), 6.99 (t, J = 7.6 Hz, 2 H), 7.17–7.27 (m, 6 H), 7.36 (d, J = 8 Hz, 2 H).

Bis(2-methylindol-3-yl)(phenyl)methane (3a)²⁹

Pink solid; mp 246-248 °C.

¹H NMR (400 MHz, CDCl₃): δ = 1.91 (s, 6 H), 5.81 (s, 1 H), 6.57 (t, *J* = 8 Hz, 2 H), 6.74–6.79 (m, 4 H), 7.00–7.08 (m, 7 H), 8.67 (br, 2 H, NH).

(4-Methoxyphenyl)bis(2-methylindol-3-yl)methane (3b)²⁶

Pink solid; mp 99-101 °C.

¹H NMR (400 MHz, CDCl₃): δ = 2.05 (s, 6 H), 3.78 (s, 3 H), 5.93 (s, 1 H), 6.77 (d, *J* = 8.8 Hz, 2 H), 6.82 (t, *J* = 8.4 Hz, 2 H), 6.99 (d, *J* = 8.4 Hz, 2 H), 7.03 (t, *J* = 7.2 Hz, 2 H), 7.15 (d, *J* = 7.2 Hz, 2 H), 7.22 (d, *J* = 8.8 Hz, 2 H), 7.7 (br, 2 H, NH).

Bis(5-bromoindol-3-yl)(phenyl)methane (4)¹⁰

Red solid; mp 246-248 °C.

¹H NMR (400 MHz, CDCl₃): δ = 5.73 (s, 1 H), 6.62 (s, 2 H), 7.16–7.28 (m, 9 H), 7.45 (s, 2 H), 7.97 (br, 2 H, NH).

$Bis (5-methoxy indol-3-yl) (phenyl) methane \ (5)^{30}$

Pink solid; mp 218-220 °C

 ^1H NMR (400 MHz, CDCl_3): δ = 2.67 (s, 6 H), 5.75 (s, 1 H), 6.64 (s, 2 H), 6.78–6.82 (m, 4 H), 7.21–7.34 (m, 7 H), 7.8 (br, 2 H, NH).

Bis(7-ethylindol-3-yl)(phenyl)methane (6)

Red solid; mp 97-99 °C

¹H NMR (400 MHz, CDCl₃): δ = 1.40 (q, *J* = 7.6 Hz, 6 H), 2.83 (t, *J* = 7.6 Hz, 4 H), 5.92 (s, 1 H), 6.39 (s, 2 H), 7.08–7.10 (m, 4 H), 7.32–7.40 (m, 7 H), 7.5 (br, 2 H, NH).

¹³C NMR (100 MHz, CDCl₃): δ = 13, 23, 40, 117, 119, 120, 123, 124, 126, 128, 135, 144.

ESI-HRMS: m/z [M + Na] calcd for C₂₇H₂₆N₂: 401.1994; found: 401.1985.

3,3',3'''-(1,4-Phenylenedimethanetriyl)tetrakis(1*H***-indole) (7)⁷**

Orange-red solid; mp 139 -141 °C

¹H NMR (400 MHz, CDCl₃): δ = 5.81 (s, 2 H), 6.60 (s, 4 H), 6.90 (t, *J* = 6 Hz, 4 H), 7.11 (t, *J* = 6 Hz, 4 H), 7.28 (d, *J* = 6 Hz, 4 H), 7.36 (d, *J* = 6 Hz, 4 H), 8.32 (br, 4 H, NH).

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