Chapter 2

Persulfate Mediated Synthesis of Diindolylmethanes from Coupling of Alcohols with Indoles

2. Persulfate Mediated Synthesis of Diindolylmethanes from Coupling of Alcohols with Indoles

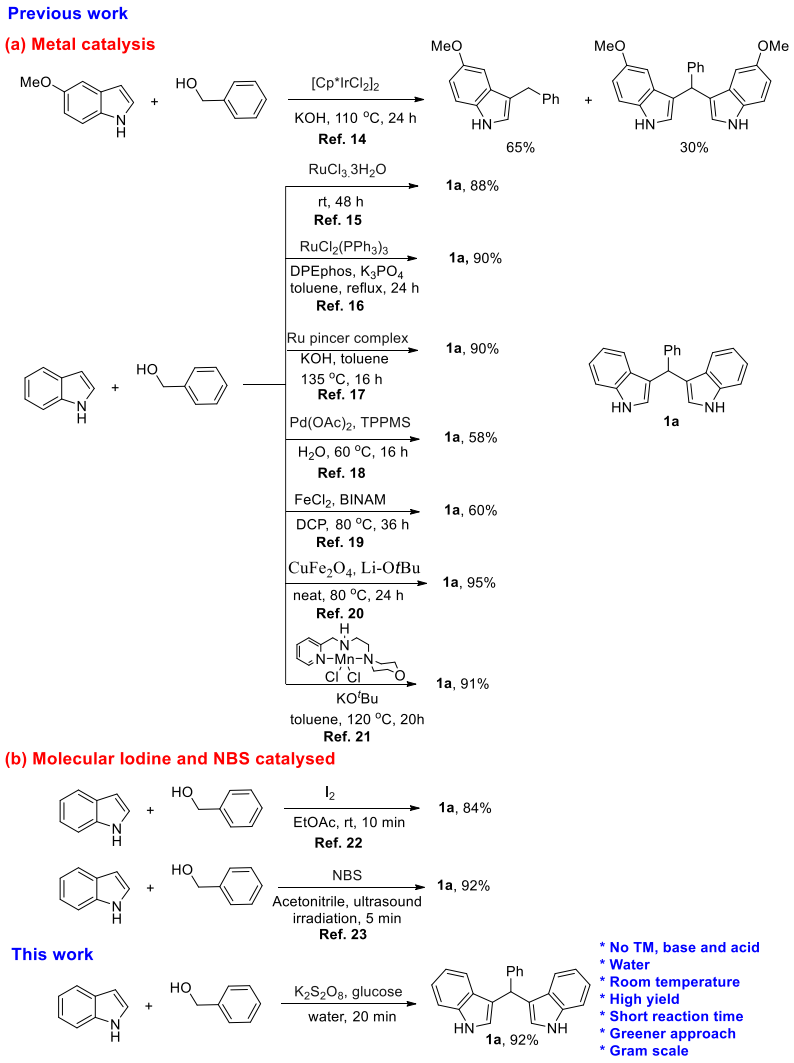
2.1 Introduction

Bis(indolyl)methanes (BIMs) are key units in bioactive metabolites of cruciferous plants, marine, and terrestrial microorganisms[1] e.g., vibrindole A from *Vibrio parahaemolyticus*[2], arsindoline A[3] and arsinoline B[4] from bacterium strain *CB101*.[5] BIMs exhibit various bioactivities such as anticancer[1], fibromyalgia treatment[6], antistaphylococcal[7], antileishmanial[8], antioxidant.[9] Because of their biological importance, several efficient methods for their syntheses have been developed.[3,10–19]

The general synthetic route involves the electrophilic substitution reaction of indoles with carbonyl compounds using appropriate catalysts,[10-15] but there are few reports for oxidative coupling of alcohols and indoles to generate BIMs (scheme 2.1). Keep *et al.* performed iridium(III)-catalyzed reactions of indoles with alcohols for C-3 alkylation and received BIM as minor by products.[20] Liu and coworkers used $RuCl_3 \cdot 3H_2O$ catalyst for one-pot synthesis of BIM from benzylic alcohols with indoles.[21] Ohta *et al.* performed $RuCl_3(PPh_3)_3$ catalyzed BIM synthesis from indoles and benzylic alcohols in 24 h at 110 °C.[22] Srimani's group used ruthenium pincer complex for transformation of indoles and alcohols to get BIMs.[23] Yokoyama *et al.* reported palladium-triggered domino reactions between indoles and benzyl alcohols to afford BIMs but it required 16 h for completion of reaction.[24] Sekar and group used $FeCl_2$/BINAM complex for domino synthesis of BIM from indoles and primary alcohols.[25] Vu *et al.* used $CuFe_2O_4$ as recyclable magnetic catalyst with Li-O*t*Bu to synthesize BIM at 80 °C.[26] Balaram *et al.* [27] performed dehydrogenative coupling of alcohols with indoles using air-stable NNN-Mn(II) pincer complex in 20 h at 120 °C. Itoh *et al.* performed synthesis of BIM from indoles and benzyl alcohols under visible light irradiation using iodine

in 20 h.[28] Chabukswar *et al.* reported use of *N*-bromosuccinimide for synthesis of BIM from primary alcohols under ultrasound irradiation.[29] (Scheme 2.1) As evident from the available records, most of these methods involve use of transition metals, application of high temperatures and longer reaction time. Thus, a simplified, mild, and basic protocol to yield BIM from alcohol is highly desirable.

Scheme 2.1: Synthetic approaches toward BIMs.



Persulfate ($S_2O_8^{2-}$) is a commercially available oxidizing agent and has been extensively involved in a wide array of oxidative organic transformations and oxidation of environmental contaminates.[30-39] In literature, use of $K_2S_2O_8$-Brönsted ionic liquid ([Hmim]-CH_3SO_3)[40] and

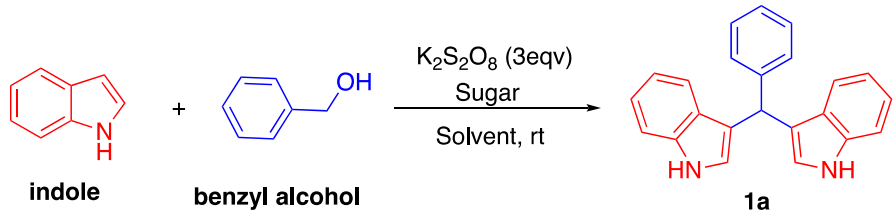
$K_2S_2O_8$-activated charcoal[41] for specific oxidation of alcohols to carbonyl analogues have been reported. To the best of our knowledge, we have found only one report where $K_2S_2O_8$-glucose has been used for the synthesis of diverse heterocycles.[42] Herein, we have disclosed the application of $K_2S_2O_8$-glucose system for *in situ* conversion of alcohol to carbonyl condensation with indoles for synthesis of BIMs. The reaction is conducted in water at room temperature. The method does not involve any use of a transition metal, base, or acid. It shows a broad substrate scope and gram-scalable ability. Finally, a possible mechanism is proposed for the synthesis.

2.2 Results and discussion

To find out the optimum reaction conditions, we have screened various reaction parameters employing indole and benzyl alcohol as model substrates. Indole (1 equiv.) was reacted with benzyl alcohol (1 equiv.) in the presence of $K_2S_2O_8$ (3 equiv.) in acetonitrile at room temperature for 12 h, which did not result in the formation of **1a**, suggesting persulfate was not activated at room temperature (Table 1, entry 1). However, the addition of glucose (1 equiv.) under the same conditions yielded **1a** in 27% yield (entry 2). Solvent screening indicated that the solubility of glucose was optimal in water, resulted 92% yield of **1a** (entry 4). Changing the sugar from glucose to galactose, lactose, chitosan, raffinose, or starch gave **1a** with variable yields (35-78%, entries 5-9). Lowering the equivalent of glucose gave **1a**, however in a somewhat reduced yield (81%, entry 10).

Table 2.1: Optimization of the reaction condition for synthesis of BIM.[a]

Tbale 2. 1



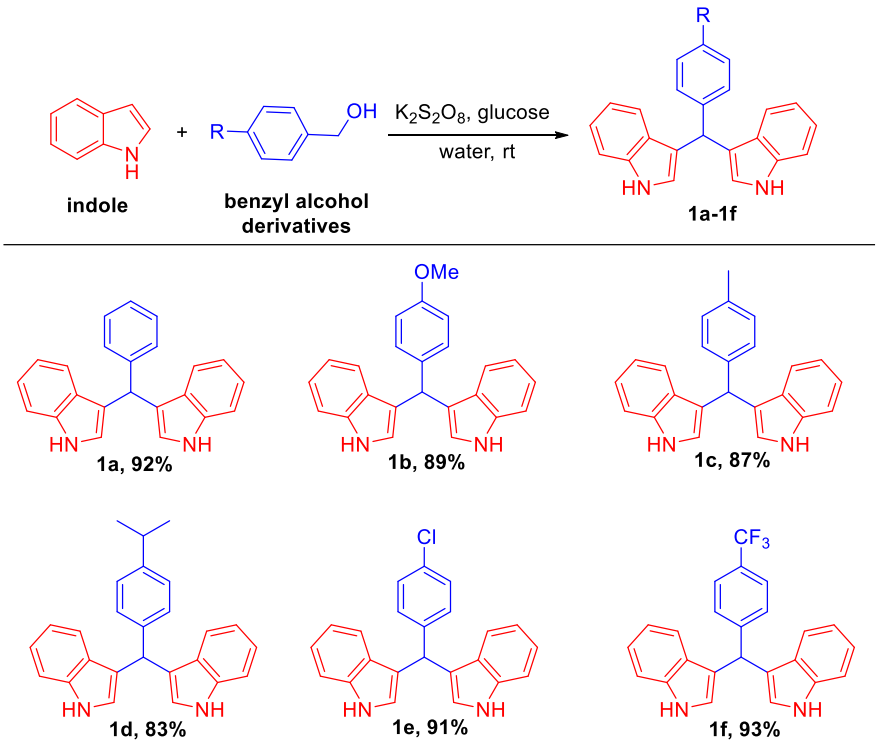
S. No.	Sugar	Solvent	Time (h)	%Yield[b]
1	-	ACN	12	0
2	Glucose (1 equiv.)	ACN	12	27
3	Glucose (1 equiv.)	ACN:H_2O	1	76
4	Glucose (1 equiv.)	H_2O	0.20	92
5	Galactose	H_2O	0.20	78
6	Lactose	H_2O	0.20	64
7	Chitosan	H_2O	0.20	45
8	Raffinose	H_2O	0.20	43
9	Starch	H_2O	0.20	35
10	Glucose (0.75) equiv.)	H_2O	0.20	81

[a]Reaction conditions: indole (1 mmol), benzyl alcohol (1 mmol), $K_2S_2O_8$ (3 equiv.), solvent (5 mL), room temp. [b]Isolated yield (%).

After optimization of the protocol, we explored the scope of the various substituted benzyl alcohols in synthesis of BIM (scheme 2.2). Benzyl alcohols substituted with electron-donating

(-Me, -OMe, and -*i*Pr) or electron-withdrawing (-Cl, and -CF_3,) groups resulted BIMs in good yields (**1a-1f**, 83–93%).

Scheme 2.2: Substrate scope with various substituted benzyl alcohols.

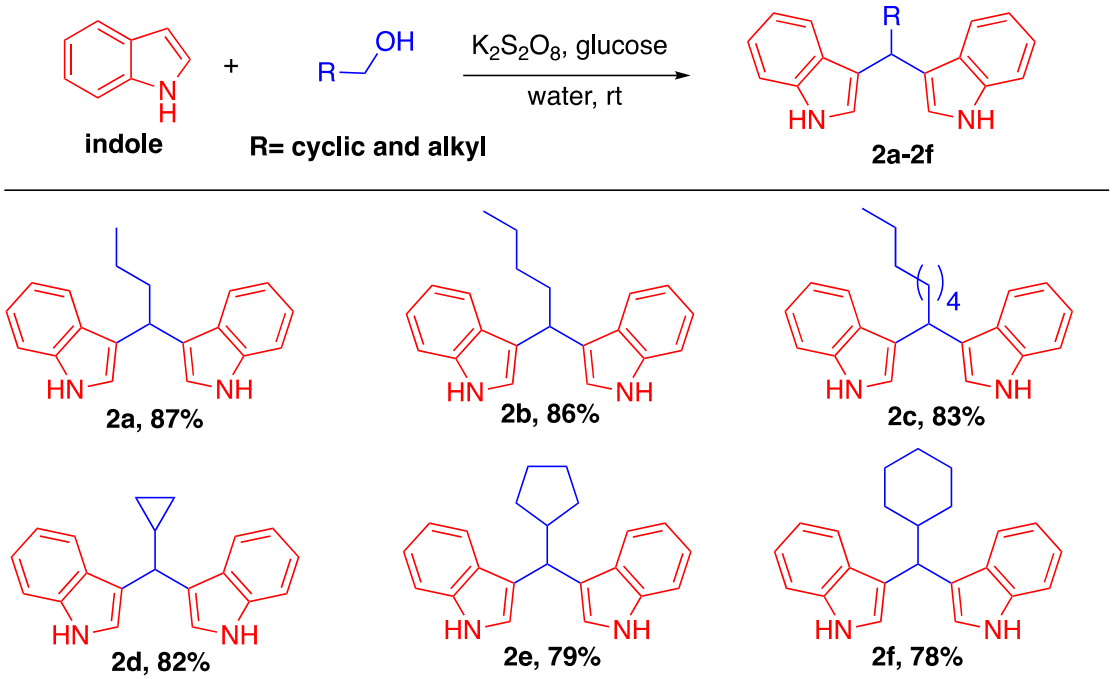


[a]Reaction conditions: indole (1 mmol), benzyl alcohol (1 mmol), $K_2S_2O_8$ (3 equiv.), glucose (1 equiv.), water (5 mL), room temp., 20 min.

The *in situ* oxidation of alkyl alcohols is challenging compared to benzyl alcohol. Recently, Nguyen and coworkers[26] received 77-83% yield of BIMs containing aliphatic alkyl groups with $CuFe_2O_4$ heterogeneous catalyst under harsh condition (120 °C, 24 h). We explored the scope of aliphatic alcohols with the optimized condition in hand (scheme 2.3). Fortunately, we have received 83-87% yields of BIM containing acyclic alkyl groups (**2a-2c**). Furthermore, more challenging cycloalkylmethanols were also examined.

Cyclopropanemethanol, cyclopentanemethanol, and cyclohexanemethanol showed good performance in synthesis of BIM **2d** (82%), **2e** (79%), and **2f** (78%), respectively.

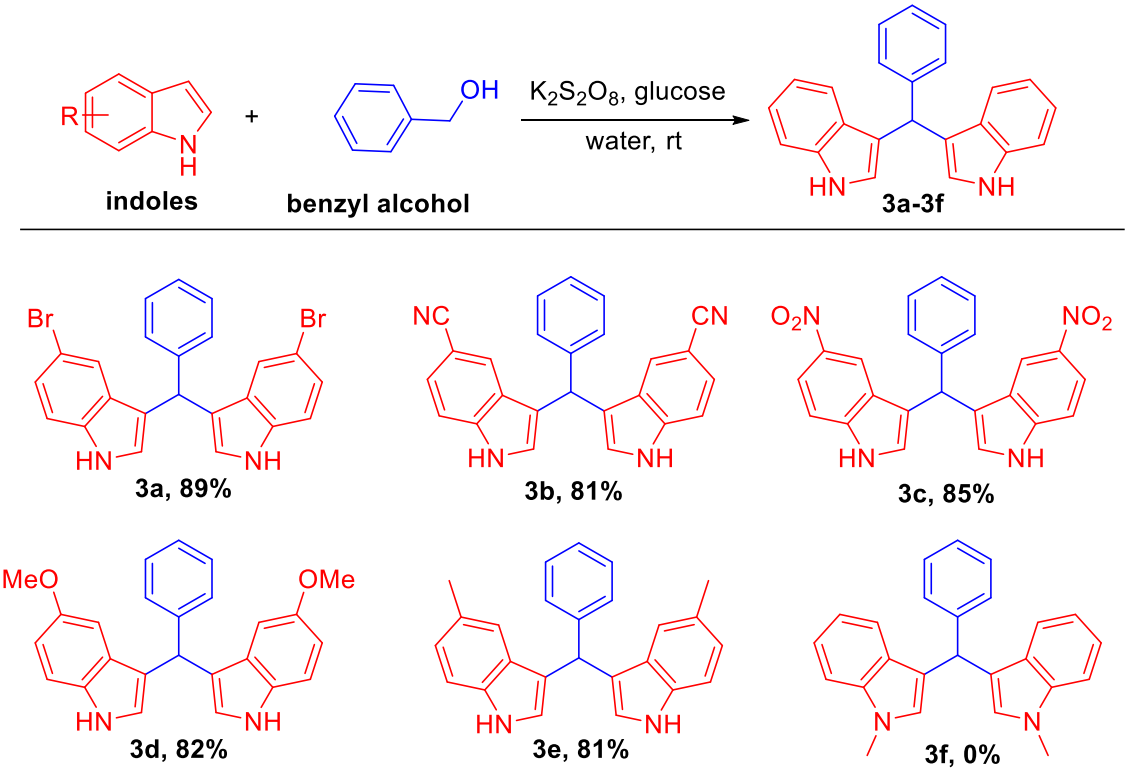
Scheme 2.3: Substrates scope with various alkyl alcohols.



[a]Reaction conditions: indole (1 mmol), alky alcohol (1 mmol), $K_2S_2O_8$ (3 equiv.), glucose (1 equiv.), water (5 mL), room temp., 20 min.

Indoles bearing electron withdrawing groups (-Br, -CN, $-NO_2$) and electron donating groups (-OMe and -Me) were well tolerated under standardized reaction conditions with benzyl alcohol and gave high yields of the BIMs **3a**-**3e** (81-89%, scheme 2.4).

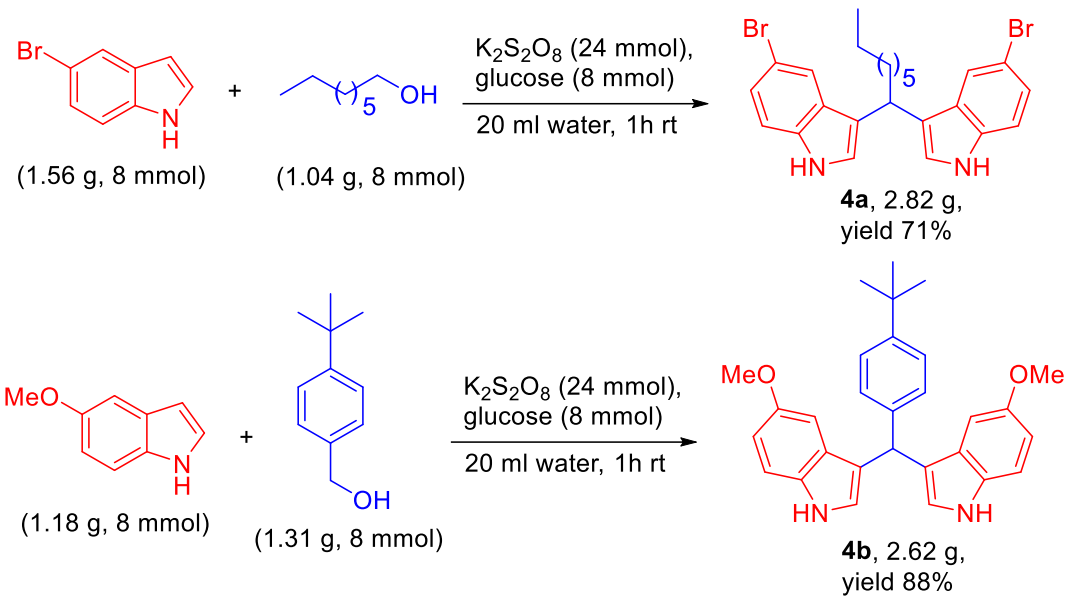
Scheme 2.4: Substrates scope with various substituted indoles.



[a]Reaction conditions: indole (1 mmol), alky alcohol (2 mmol), $K_2S_2O_8$ (3 equiv.), glucose (1 equiv.), water (5 mL), room temp., 20 min.

Compound **4a** has been reported in literature to induce apoptosis by upregulating pro-apoptotic prostate apoptosis response 4 (Par-4) and suppression of expression of pro-survival glucose-regulated protein 78 (GRP78).[43] Compound **4b** has been reported as a potent inhibitor of *Staphylococcus aureus*, MRSA and VRE.[44] We have successfully demonstrated the practical application of our method in gram scale synthesis of **4a** and **4b**. The yield of compounds **4a** and **4b** were found to be in 71% and 88% yield, respectively (Scheme 2.5).

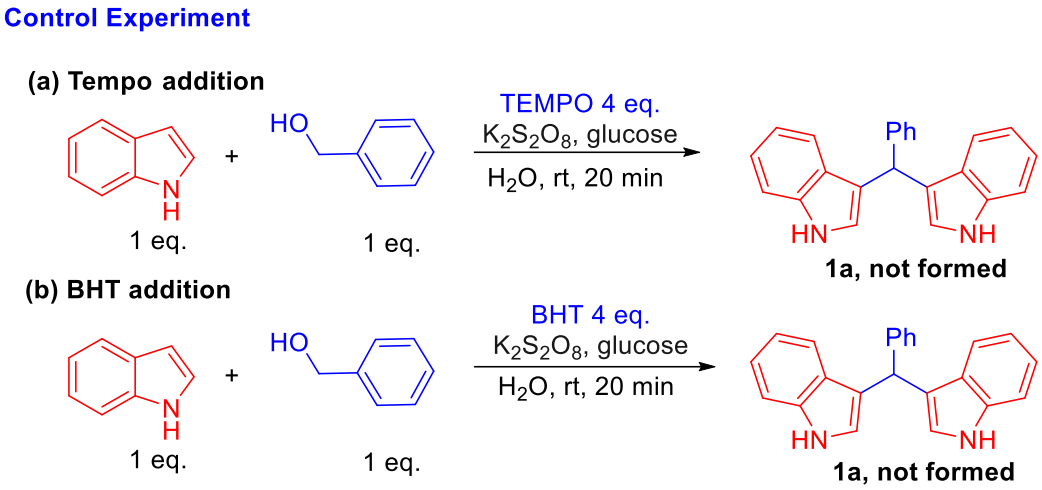
Scheme 2.5: Gram scale experiment.



2.3 Control experiments

Reaction mechanism was affirmed using several control experiments. Compound **1a** was not formed, when 4.0 equiv. of *2,2,6,6*-tetramethylpiperidinooxy (TEMPO) or *2,6*-di*tert*-butyl-4-methylphenol (BHT) was added to the reaction under standard conditions (scheme 2.6). These results indicate that a radical mechanism may involve converting alcohol to carbonyl compounds. When indole was replaced by *N*-methyl indole, expected product **3f** (scheme 2.4) was not formed. The result indicates the formation of nitrogen radical on N-H bond which then undergoes 1,3-*H* shift to form carbon radical.

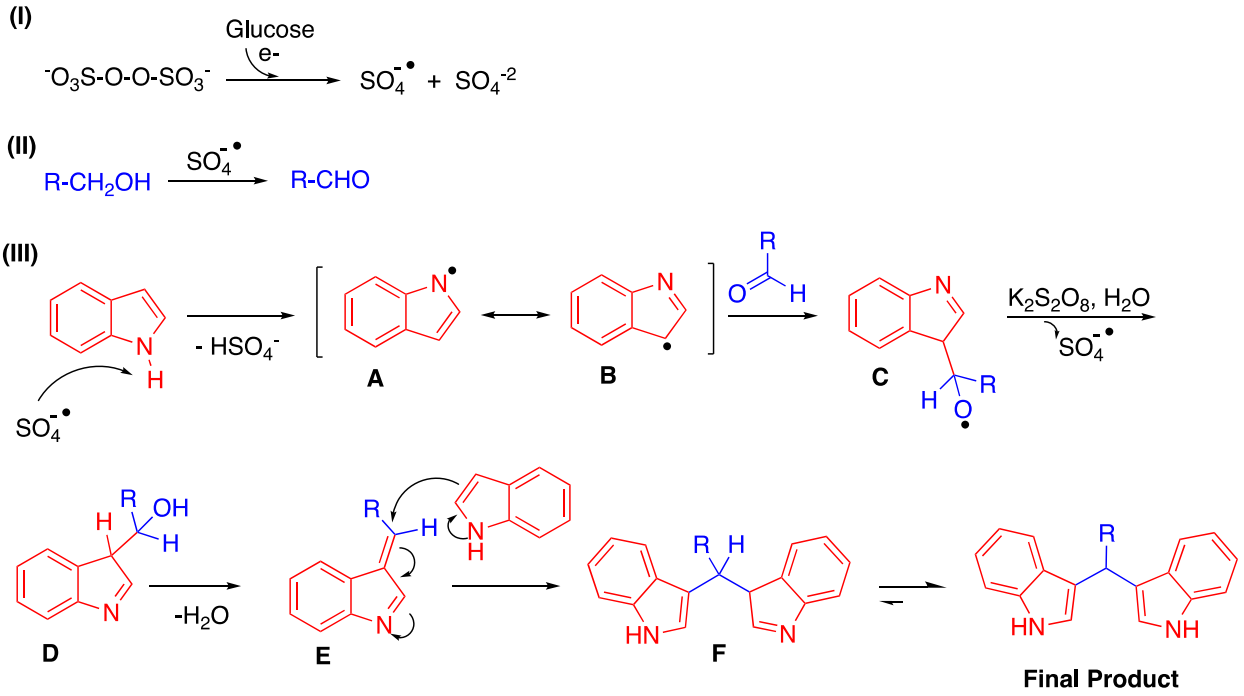
Scheme 2.6: Control experiments.



Reaction conditions: (a) indole (1 mmol), benzyl alcohol (1 mmol), TEMPO (4 equiv.), $K_2S_2O_8$ (3 equiv.), glucose (1 equiv.), water (5 mL), room temp. 20 min.; (b) indole (1 mmol), benzyl alcohol (1 mmol), BHT (4 equiv.), $K_2S_2O_8$ (3 equiv.), glucose (1 equiv.), water (5 mL), room temp. 20 min.

Based upon the inferences drawn from control experiments and literature review,[21, 37, 40] we propose a plausible mechanism, as depicted in scheme 2.7. Glucose transfers one electron to $S_2O_8^{2-}$ which causes heterolytic cleavage at peroxy linkage to generate $SO_4^{\cdot-}$ radical (I, Scheme 2.7).[3] The generated radical performs oxidation of alcohol to aldehyde (II, scheme 2.7).[41] Also, $SO_4^{\cdot-}$ attacks the indole to form nitrogen radical **A** and HSO_4^-. **A** undergoes 1,3-*H* shift and isomerizes to carbon radical **B**, which reacts with carbonyl compound to generate oxygen radical **C**, which reacts with $K_2S_2O_8$ and H_2O to generate $SO_4^{\cdot-}$ and **D**. *β*-elimination of **D** generates intermediate **E**. Another indole ring then reacts with **E** to form **F** that gradually isomerizes to give final product (III, scheme 2.7).[13]

Scheme 2.7: Possible Reaction Mechanism.



2.4 Conclusion

In summary, we have developed green strategy for the synthesis of bisindolylmethane using inexpensive $K_2S_2O_8$ at room temperature in water. The *in situ* generated $SO_4^{\cdot-}$ radical from $K_2S_2O_8$ readily oxidise alcohol to carbonyl compounds and subsequent condensation with indoles results BIMs in good yield. Variety of benzyl-/aliphatic alcohols and indoles are well tolerated in this protocol and gives BIMs in high yields. The yield of the gram-scale synthesis could be up to 90%. Efforts to expand the utility of $K_2S_2O_8$-glucose to construct C-C bonds are currently in progress.

2.5 General procedure for the synthesis of 1a-3f

An oven-dried screw cap vial was charged with indoles (1 mmol), benzyl/alkyl alcohols (1 mmol), $K_2S_2O_8$ (3 mmol) and glucose (1 mmol) in water (5 ml). The resulting solution was stirred at room temperature for 0.20 h. The reaction mixture was diluted with water (5 mL),

then extracted with ethyl acetate (15 mL × 3). After drying with anhydrous Na_2SO_4, the organic phase was evaporated to dryness and purified by column chromatography using ethyl acetate:hexane

2.6 Gram Scale procedure for the synthesis

2.6.1 Synthesis for the compound 4a: A round bottom flask was charged with 5-bromo indole (1.56 g, 8 mmol), octanol (1.04 g, 8 mmol), $K_2S_2O_8$ (6.48g, 24 mmol) and glucose (1.4g, 8 mmol) in water (20 ml). The resulting solution was stirred at room temperature for 1 h. The reaction mixture was diluted with water (20 mL), then extracted with ethyl acetate (40 mL × 3). After drying with anhydrous Na2SO4, the organic phase was evaporated to dryness and purified by column chromatography using 30 % ethyl acetate:hexane. Compound 4a was obtained as a red solid (2.82 g, 71% yield).

2.6.2 Synthesis for the compound 4b: A round bottom flask was charged with 5-methoxyindole (1.18 g, 8 mmol), 4-(*tert*-butyl)phenyl)methanol (1.31 g, 8 mmol), $K_2S_2O_8$ (6.48 g, 24 mmol) and glucose (1.4 g, 8 mmol) in water (20 ml). The resulting solution was stirred at room temperature for 1 h. The reaction mixture was diluted with water (20 mL), then extracted with ethyl acetate (40 mL × 3). After drying with anhydrous Na_2SO_4, the organic phase was evaporated to dryness and purified by column chromatography using 40 % ethyl acetate:hexane. Compound 4b was obtained as a red solid (2.62 g, 88% yield).

2.7. Control experiment procedure

2.7.1 TEMPO addition in general procedure

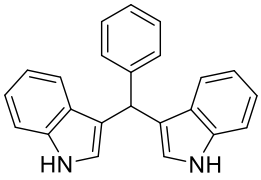
A screw cap vial was charged with indole (117 mg, 1 mmol), benzyl alcohol (108 mg, 1 mmol), $K_2S_2O_8$ (810 mg, 3 mmol), TEMPO (624 mg, 4 mmol) and glucose (180 mg, 1mmol)

in water (5 ml). The resulting solution was stirred at room temperature for 0.20 h. We have not observed formation of product **1a**.

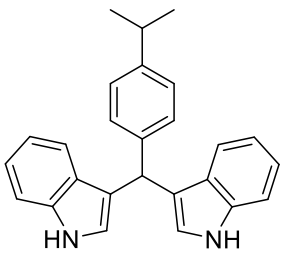
2.7.2 BHT addition in general procedure

A screw cap vial was charged with indole (117 mg, 1 mmol), benzyl alcohol (108 mg, 1 mmol), $K_2S_2O_8$ (810 mg, 3 mmol), BHT (880 mg, 4 mmol) and glucose (180 mg, 1mmol) in water (5 ml). The resulting solution was stirred at room temperature for 0.20 h. We have not observed formation of product **1a**.

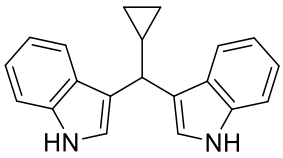
2.8 Analytical Data of Compounds



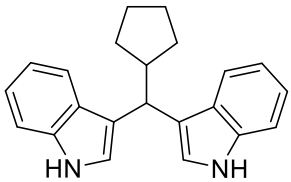
3,3'-(phenylmethylene)bis(1H-indole) (1a): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 40% ethyl acetate:hexane. Compound **1a** was obtained as a brown solid with 92% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 2H), 7.44-7.19 (m, 11H), 7.04 (t, *J* = 7.5 Hz, 2H), 6.64 (s, 2H), 5.92 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.1, 136.7, 128.7, 128.2, 127.1, 126.2, 123.7, 121.9, 119.9, 119.7, 119.2, 111.1, 40.2.



3,3'-((4-isopropylphenyl)methylene)bis(1H-indole) (1d): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 40% ethyl acetate:hexane. Compound **1d** was obtained as a red solid with 83 % yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (s, 2H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.20-7.15 (m, 4H), 7.04-7.02 (m, 2H), 6.67 (d, *J* = 1.8 Hz, 2H), 5.89 (s, 1H), 2.94-2.87 (m, 1H), 1.27 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.5, 141.2, 136.7, 128.5, 127.1, 126.2, 123.6, 121.9, 120.0, 120.1, 111.0, 39.7, 33.7, 24.1.

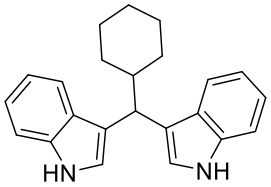


3,3'-(cyclopropylmethylene)bis(1H-indole) (2d): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 30% ethyl acetate:hexane. Compound **2d** was obtained as a red solid with 82 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.22-7.19 (m, 2H), 7.08-7.04 (m, 4H), 4.04 (d, *J* = 8.0 Hz, 1H), 1.63-1.58 (s, 1H), 0.70-0.67 (m, 2H), 0.46-0.43 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 127.3, 122.1, 121.7, 120.1, 119.9, 119.1, 111.1, 38.2, 16.8, 4.9.

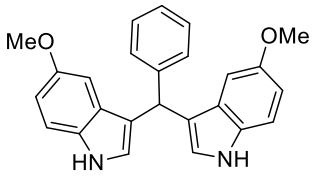


3,3'-(cyclopentylmethylene)bis(1H-indole) (2e): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 30% ethyl acetate:hexane. Compound **2e** was obtained as a red solid with 79 % yield.

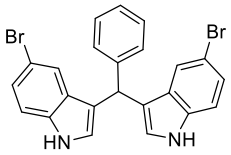
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.18-7.15 (m, 2H), 7.10-7.07 (m, 4H), 4.32 (d, *J* = 10.0 Hz, 1H), 2.96-2.87 (m, 1H), 1.83-1.80 (m, 2H), 1.70-1.59 (m, 4H), 1.48-1.41 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 127.5. 121.6, 121.5, 120.7, 119.6, 118.9, 111.0, 45.3, 39.5, 32.4, 25.6.



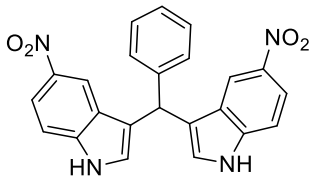
3,3'-(cyclohexylmethylene)bis(1H-indole) (2f): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 30% ethyl acetate:hexane. Compound **2f** was obtained as a red solid with 78 % yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (s, 2H), 7.69 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.17-7.15 (m, 2H), 7.10-7.17 (m, 4H), 4.30 (d, *J* = 9.0 Hz, 1H), 2.30-2.25 (m, 1H), 1.87-1.86 (m, 2H), 1.71-1.65 (m, 4H), 1.29-1.23 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.2, 127.8, 121.6, 121.61, 119.7, 119.6, 119.0, 111.0, 42.9, 40.1, 32.4, 26.7, 26.71.



3,3'-(phenylmethylene)bis(5-methoxy-1H-indole) (3d): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 50%. ethyl acetate:hexane. Compound **3d** was obtained as a red colour solid with 82% yield. ^{1}H NMR (500 MHz, DMSO- d_6) δ 10.61 (s, 2H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.27-7.23 (m, 4H), 7.17-7.14 (m, 1H), 6.81 (d, *J* = 2.0 Hz, 2H), 6.70-6.68 (m, 4H), 5.71 (s, 1H), 3.57 (s, 6H). ^{13}C NMR (126 MHz, DMSO- d_6) δ 153.1, 145.3, 132.2, 128.7, 128.5, 127.4, 126.3, 124.7, 118.1, 112.6, 111.0, 101.9, 55.7, 40.07.

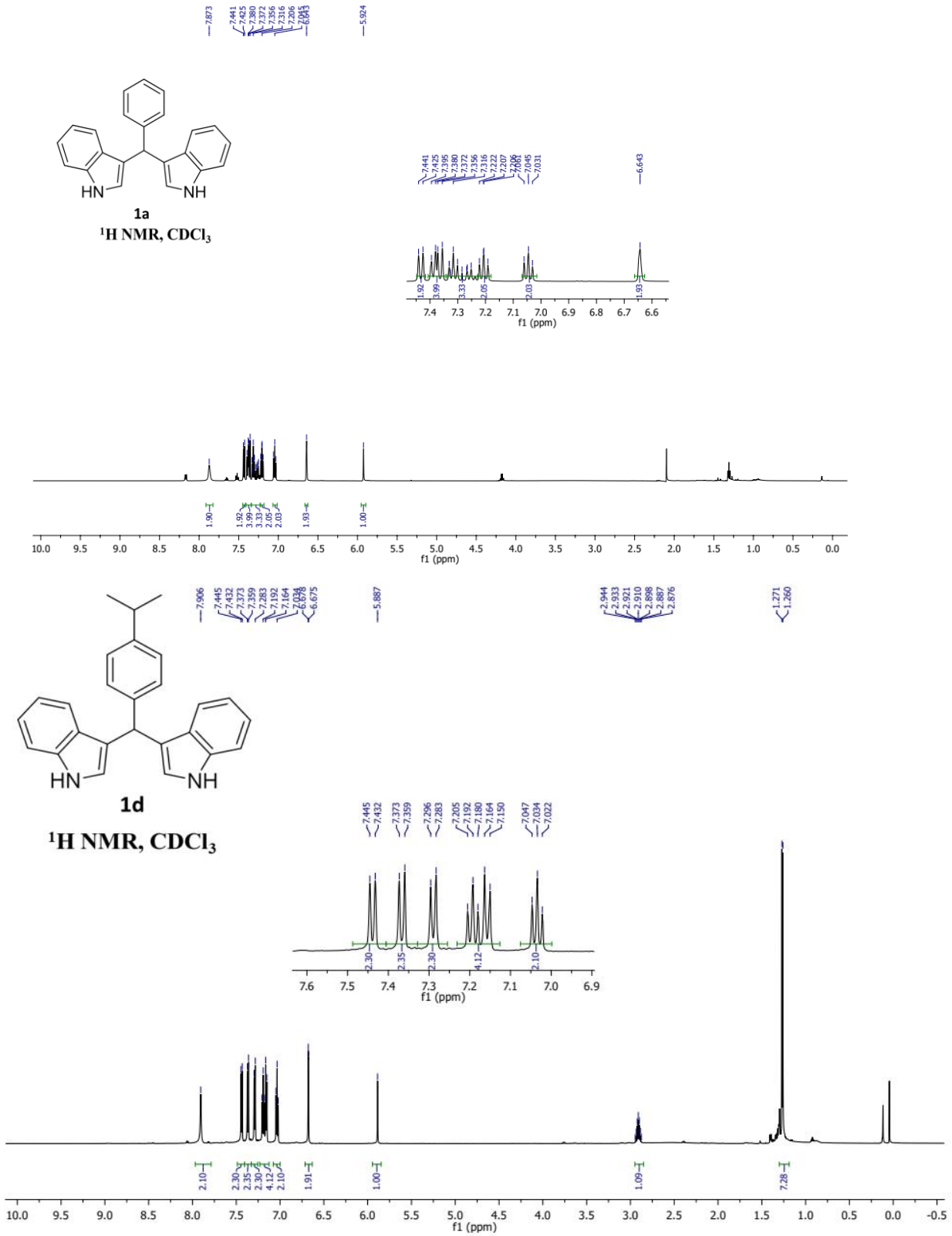


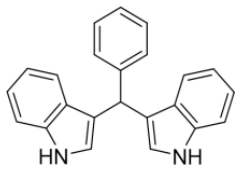
3,3'-(phenylmethylene)bis(5-bromo-1H-indole) (3a) : The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 40% ethyl acetate:hexane. Compound **3d** was obtained as a red colour solid with 89% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.08 (d, *J* = 2.0 Hz, 2H), 7.42 (d, *J* = 1.5 Hz, 2H), 7.38 (d, *J* = 9.0 Hz, 2H), 7.32-7.28 (m, 4H), 7.22-7.16 (m, 3H), 6.88 (d, *J* = 2.5 Hz, 2H), 5.82 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2, 140.4, 133.5, 133.3, 131.41, 130.4, 128.8, 126.4, 126.3, 122.8, 118.9, 116.2, 44.2.



3,3'-(phenylmethylene)bis(5-nitro-1H-indole) (3c): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 40% ethyl acetate:hexane. Compound **3c** was obtained as a yellow solid with 85% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.69 (s, 2H), 8.31 (d, J = 2 Hz, 2H), 7 .99-7.96 (m, 2H), 7.55 (d, J = 9.0 Hz, 2H), 7.41 (d, J = 7.5 Hz, 2H), 7.33-7.30 (m, 2H), 7.23-7.20 (m, 1H), 7.13 (d, J = 1.5 Hz, 2H), 6.19 (s, 1H). 13 C NMR (126 MHz, DMSO-d_6) δ 144.2, 140.6, 140.2,128.9, 128.6, 128.0, 126.9, 126.2, 121.0, 117.1, 116.7, 112.6, 38.9.

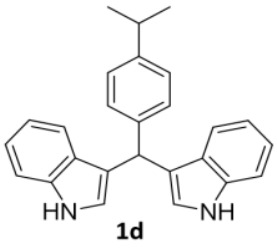
2.9 Spectral Data of Synthesized Products





1a

^{13}C NMR, $CDCl_3$



1d

^{13}C NMR, $CDCl_3$

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