RESEARCH ARTICLE



Water-Mediated Green and Efficient Synthesis of Bis(Indolyl)methanes Using Ammonium Iron(II) Sulfate



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ARTICLE HISTORY

Received: December 29, 2018 Revised: April 15, 2019 Accepted: April 18, 2019 **Abstract:** An efficient protocol for the synthesis of symmetrical 3,3'-bis(indolyl)arylmethanes catalyzed by green and easily available ammonium iron(II) sulfate (Mohr's salt) has been developed in "green" water solvent afforded in excellent yield.

DOI: 10.2174/1570178616666190522121135



Keywords: Water, catalysis, Bis(indolyl)methanes, green chemistry, ammonium iron(II) sulfate, Indole.

1. INTRODUCTION

Indoles are most feasible imperative motif among heterocyclic scaffolds owing to their existence in diverse natural commodities, agrochemicals and pharmaceuticals [1-3]. Especially, the nitrogen-containing 3,3'-bis(indolyl)methanes (BIMs) of two indole motifs united by a single carbon at 3position are the well-known class of alkaloids, [4] have been frequently found in marine [5-9] and terrestrial [10-12] origins. For the variety of biological applications, their structure has been proven to be constructive in search of new therapeutic agents [13]. By virtue of their prominence in natural capitals and the diversity of biological performance, BIMs are essential building block having prominent recognition and intensifying appeal in the development of green synthetic routes. The methods accounted for the synthesis of substituted BIMs by condensation of indoles with carbonyl compounds or their synthetic equivalents in the presence of an acid or base [14-34]. The expanding awareness of greener, more sustainable technologies has directed wakefulness on the adoption of efficient catalytic methodologies for the manufacture of fine chemicals and pharmaceuticals. Another facet of the growing recognition for alternative reaction media circumvents the disputes accompanied by prevailing volatile organic solvents. The manifesto of nonconventional reaction media brings convenience for promoting the improvement and recycling of the catalyst. The ultimate in clean catalytic technologies is to produce an interesting approach in an aqueous media for green, sustainable organic synthesis. Interestingly, Mohr's salt is more favorable over other iron salts because of somewhat labile to oxidation by air to iron (III) in an enormous breadth, tuning prime attention to the field of catalysis for organic transformations [35]. Here, we are extending our efforts towards the construction of 3,3'-bis(indolyl)arylmethanes using an environmentally benign water medium in the presence of catalytic amount of ammonium iron(II) sulfate (Mohr's salt).

2. RESULTS AND DISCUSSION

At the outset, we started the reaction between 4methoxybenzaldehyde 1a (1 mmol) and indole 2 (2 mmol) in the presence of 5 mole % of Ammonium Ferrous Sulphate (Mohr's salt) catalyst at room temperature using toluene as reaction medium afforded 3,3'-((4-methoxyphenyl)methylene)bis(1H-indole) 3a in 38% yield after 12 h (entry 1, Table 1). In a further study, the reaction carried out using different non-polar solvents such as chlorobenzene, DCM and DCE also obtained 3a in yields such as 35%, 25%, and 46% (entries 2-4, Table 1). The reaction was carried out to a greater extent in order to improve the yield of anticipated product in divergent polar solvents like EtOH, i-PrOH, n-BuOH, and MeOH at room temperature and product 3a furnished in 45%, 40%, 30% and 60%, yields correspondingly (entries 5-8, Table 1). Interestingly, under favorable optimization using MeOH up to 60%, the reaction attempted in H₂O medium and product 3a was afforded in 65% yield (entry 9, Table 1). Similarly, the reaction was executed under reflux condition using H₂O medium in which 3,3'-((4methoxyphenyl)methylene)bis(1H-indole) 3a procured in excellent yield up to 88% within 3.5 h (entry 10, Table 1). Furthermore, catalyst loading was accomplished to evaluate the well-optimized condition for 7 mole % where 3a produced 92% yield in 3.5 h (entry 11, Table 1) and the same

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Table 1. Optimization of reaction conditions^a.

	MeO H +	$ \begin{array}{c} \overbrace{\begin{array}{c}} \overbrace{\begin{array}{c}} \overbrace{\begin{array}{c}} \overbrace{\begin{array}{c}} \overbrace{\begin{array}{c}} I\end{array}}\\H\end{array}} & \frac{(NH_4)_2 Fe(I)}{sc}\\ sc\\ z\end{array} $	SO ₄) ₂ .6H ₂ O	OMe N H 3a	
Entry	Solvent	Catalyst (mol %)	Temp (°C)	Time (h)	Yield ^b (%)
1	Toluene	5	r.t.	24	30
2	Chlorobenzene	5	r.t.	24	34
3	DCM	5	r.t.	24	25
4	DCE	5	r.t.	24	38
5	EtOH	5	r.t.	48	45
6	i-PrOH	5	r.t.	48	40
7	n-BuOH	5	r.t.	48	30
8	MeOH	5	r.t.	24	60
9	H ₂ O	5	r.t.	24	65
10	H ₂ O	5	reflux	3.5	88
11	H ₂ O	7	reflux	3.5	92
12	H ₂ O	10	reflux	3.5	92
13	H ₂ O	2	reflux	6.0	80

^aReaction conditions: **1a** (1.2 mmol), **2a** (2.0 mmol), solvent (5 mL). ^bIsolated yield.

result was obtained by further increasing catalyst loading up to 10 mole % (entry 12, Table 1). On the other hand, the decrease in catalyst loading from 5 mole % to 2 mole % offered anticipated product 3a in lower yield of up to 80% in 6 h (entry 13, Table 1).

With the optimized condition, the substrate scope of substituted aromatic aldehydes and indoles illustrated is shown in Table 2. The substrates containing electron-donating *i.e.* –Me, –OH and –OMe groups were well-tolerated and produced the desired products in moderate to excellent yields. Along with the electron-withdrawing *i.e.* –CN, –NO₂ groups were found competent offering the corresponding products in excellent yields. Noticeably, the halogen substituents were unharmed after the reaction, leading to construction of more halogenated derivatives of BIMs.

We proposed cautious reaction mechanism for the synthesis of bis(indolyl)methanes from benzaldehyde 1 and indole 2a using environmentally benign water medium as represented in Scheme (1). At first, the protonation using Mohr's salt at carbonyl oxygen of aldehydes generates a driving force for electrophilic substitution reaction with indole molecule **2a** towards construction of C-3 alkylated intermediate **4**. In a further step, intermediate **4** undergoes dehydration, resulted in to the formation of azafulvene intermediate **5**, which reacts with another molecule of indole **2a** leading to formation of 3,3'-bis(indolyl)methanes **3**.

3. EXPERIMENTAL SECTION

3.1. General Information

¹H and ¹³C spectra were recorded at 400 and 100 MHz respectively. Chemical shifts were reported in parts per million (ppm) downfield from an internal TMS (tetramethylsilane) reference. Coupling constants (*J*) were reported in hertz (Hz), and spin multiplicities represented by the symbol s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), p (pentet) and m (multiplet). Aromatic ring C-s of different aldehydes in the 4-substituted cases numbered as C11, C12, C13 and C14, and in the 2-substituted or other cases as C11, C12,

Table 2.Substrate scope^a.



Entry	R ¹	R ²	Time (h)	Yield ^b (%)	Product	M. P. (°C)	
						Observed	Reported
1	Н	Н	3.5	93	3b	139-141	140-142 [25]
2	4-OH	Н	3.5	90	3c	210-212	210-211 [26]
3	4_C1	Н	3.5	92	3d	77-79	78-80 [27]
4	4–F	Н	3.5	94	3e	71-73	73-75 [28]
5	4–CN	Н	3.0	95	3f	209-210	208-209 [29]
6	2-Cl	Н	3.5	91	3g	72-73	74-76 [25]
7	2–OMe	Н	3.5	85	3h	136-138	134-136 [30]
8	2–OH	Н	4.0	90	3i	340-342	341-343 [31]
9	2–OH, 5–Br	Н	4.0	93	3j	137-139	136-138 [32]
10	Н	Me	3.5	91	3k	246-248	247-248 [25]
11	4-OH	Me	3.5	92	31	236-238	238-240 [26]
12	4-OMe	Me	3.5	93	3m	146-148	147-150 [33]
13	4-Cl	Me	3.5	92	3n	240-242	241-243 [34]

^aReaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), (NH4)₂Fe(SO₄)₂.6H₂O (0.027 g, 7 mole %), H₂O (5 mL), at reflux condition. ^bIsolated yield.

C13, C14, C15 and C16. Bond positions were reported in reciprocal centimeters (cm⁻¹). Thin layer chromatography (TLC) was performed by using commercially prepared 0.25 mm silica plates, and visualization was observed with a short wavelength UV lamp (254 nm). All commercially available reagents were used directly without purification unless otherwise stated. All the solvents used in the reactions were distilled for purity.

3.2. General Procedure for the Synthesis of BIMs (3a-n)

To a round bottom flask, a mixture of aldehyde **1** (1.0 mmol), indole **2** (2.0 mmol), (NH₄)₂FeSO₄ (0.027 g, 7 mole %), and H₂O (5 mL) was stirred at reflux condition for appropriate time-period. The reaction progress was monitored by thin layer chromatography and the reaction mixture was cooled to room temperature after completion of the reaction. The solid crude product **3** was afforded sufficiently pure for further step by simple filtration of the reaction mixture.

3.3. Spectral Data

3.3.1. Synthesis of 3,3'-(4-methoxyphenyl)methylene) bis(1H-indole) (3a)

This compound was synthesized following the above mentioned general procedure using 4-methoxybenzaldehyde (0.136 g, 1.0 mmol), indole (0.234 g, 2.0 mmol), (NH₄)₂Fe(SO₄)_{2.6}H₂O (0.027 g, 7.0 mole %), and H₂O (5 mL). Yield: 323 mg (92%) as brown colored solid compound. Chemical Formula: C₂₄H₂₀N₂O; Molecular Weight: 352.4284; M.P.: 183-185°C (Lit. [25] 185-187°C); IR (cm⁻¹): 3408, 1609, 1507, 1455, 1416, 1337, 1300, 1242, 1173, 1124, 1092, 1027, 813, 793, 740; ¹H NMR (400 MHz, CDCl₃): δ 7.94 (br s, 2H, NH), 7.41 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.38 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.28 (d, *J* = 6.6 Hz, 2H, Ar-H), 7.19 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.03 (t, *J* = 7.5 Hz, 2H, Ar-H), 6.84 (d, *J* = 6.8 Hz, 2H, Ar-H), 6.68 (s, 2H, C2H), 5.87 (s, 1H, C10H), 3.81 (s, 3H, OCH₃) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 157.8 (C14), 136.6 (C8), 136.2



Scheme (1). Plausible reaction mechanism.

(C11), 129.6 (C12), 127.1 (C9), 123.5 (C2), 121.9 (C6), 120.0 (C5), 119.9 (C4), 119.2 (C13), 113.5 (C3), 111.0 (C7), 55.2 (OCH₃), 39.3 (C10) ppm.

3.3.2. Synthesis of 3,3'-(phenylmethylene)bis(1H-indole) (3b)

This compound was synthesized following the above mentioned general procedure using benzaldehyde (0.106 g, 1.0 mmol), indole (0.234 g, 2.0 mmol), (NH₄)₂Fe(SO₄)₂.6H₂O (0.027 g, 7.0 mole %), and H₂O (5 mL). Yield: 299 mg (93%) as pink colored solid compound; Chemical Formula: $C_{23}H_{18}N_2$; Molecular Weight: 322.4024; M. P.: 139-141°C (Lit. [25] 140-142°C); IR (cm⁻¹): 3309, 1508, 1456, 1417, 1302, 1244, 1174, 1028, 814, 792; ¹H NMR (400 MHz, CDCl₃): δ 7.85 (br s, 2H, NH), 7.45-7.19 (m, 11H, Ar-H), 7.05 (t, *J* = 8.0 Hz, 2H), 6.64 (s, 2H, C2H), 5.93 (s, 1H, C10H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 144.0 (C11), 137.7 (C8), 128.8 (C12), 128.3 (C13), 127.1 (C14), 126.2 (C9), 123.7 (C2), 121.9 (C6), 120.0 (C5), 119.2 (C4), 112.1 (C3), 111.1(C7), 40.2 (C10) ppm.

3.3.3. Synthesis of 3,3'-(4-Hydroxybenzylidene)bis(1H-indole) (3c)

The compound was synthesized following the representative procedure using 4-hydroxybenzaldehyde **1c** (1.0 mmol), indole **2a** (0.234 g, 2.0 mmol), (NH₄)₂Fe(SO₄)₂.6H₂O (0.027 g, 7.0 mole %), and H₂O (5 mL). Yield: 289 mg (90%) as pink colored solid compound. Chemical Formula: C₂₃H₁₈N₂O; Molecular Weight: 338.4018; M. P.: 210-212°C (Lit. [26] 210-211°C); IR (cm⁻¹): 3412, 2924, 2853, 1611, 1510, 1456, 1338, 1217, 1093, 786, 744, 598; ¹H NMR (400 MHz, CDCl₃): δ 7.90 (br s, 2H, NH), 7.37-7.32 (m, 4H), 7.19-7.12 (m, 4H), 6.98 (t, *J* = 6.8 Hz, 2H), 6.72 (s, 2H, C2H), 6.63 (t, *J* = 6.8 Hz, 2H), 5.81 (s, 1H, C10H), 4.80 (br s, 1H, OH) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 154.5 (C14), 136.6 (C8), 135.5 (C11), 129.4 (C12), 126.9 (C9), 123.5 (C2), 121.3 (C6), 119.7 (C5), 118.6 (C4), 119.2 (C13), 113.5 (C3), 111.0 (C7), 39.3 (C10) ppm.

3.3.4. Synthesis of 3,3'-((4-chlorophenyl)methylene)bis(1H-indole) (3d)

The compound was synthesized following the representative procedure using 4-chlorobenzaldehyde **1d** (0.140 g, 1.0 mmol), indole **2a** (0.234 g, 2.0 mmol), $(NH_4)_2Fe(SO_4)_2.6H_2O$ (0.027 g, 7.0 mole %), and H₂O (5 mL). Yield: 327 mg (92%) as pink colored solid compound. Chemical Formula: $C_{23}H_{17}CIN_2$; Molecular Weight: 356.8475; M. P.: 77-79°C (Lit. [27] 76-77°C); IR (cm⁻¹): 3411, 3055, 2923, 2848, 1617, 1417, 1337, 1089, 1013, 743; ¹H NMR (400 MHz, CDCl₃): 7.91 (br, s, 2H, NH), 7.14-7.36 (m, 8H, Ar-H), 7.02 (t, 2H, Ar-H), 6.97 (t, 2H, Ar-H), 6.63 (s, 2H, C2H), 5.86 (s, 1H, C10H); ¹³C NMR (100 MHz, CDCl₃,): δ 142.4 (C8), 136.7 (C11), 131.8 (C14), 130.0 (C12), 128.3 (C13), 126.9 (C9), 123.4 (C2), 122.1 (C6), 119.8 (C5), 119.4 (C4), 119.2 (C3), 111.0 (C7), 39.6 (C10) ppm.

3.3.5. Synthesis of 3,3'-((4-fluorophenyl)methylene)bis(1H-indole) (3e)

The compound was synthesized following the representative procedure using 4-fluorobenzaldehyde **1e** (0.124 g, 1.0 mmol), indole **2a** (0.234 g, 2.0 mmol), (NH₄)₂Fe(SO₄)₂.6H₂O (0.027 g, 7.0 mole %), and H₂O (5 mL). Yield: 319 mg (94%) as pink colored solid compound. Chemical Formula: $C_{23}H_{17}FN_2$; Molecular Weight: 340.3929; M. P.: 71-73°C (Lit. [28] 73-75°C); IR (cm⁻¹): 3413, 3056, 2926, 1603, 1506, 1456, 1217, 1094, 863, 744, 582; ¹H NMR (400 MHz, CDCl₃): δ 7.88 (br s, 2H, NH), 7.30 (d, *J* = 8.4 Hz, 4H), 7.23-7.19 (m, 2H), 7.11 (t, *J* = 6.8 Hz, 2H), 6.96-6.87 (m, 4H), 6.58 (s, 2H, C2H), 5.80 (s, 1H, C10H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 139.7 (C14), 136.7 (C8), 130.1 (C11), 130.0 (C12), 126.9 (C9), 123.5 (C2), 122.0 (C6), 119.8 (C5), 119.6 (C4), 119.3 (C13), 115.0 (C3), 111.0 (C7), 39.4 (C10) ppm.

3.3.6. Synthesis of 4-(di(1H-indol-3-yl)methyl)benzonitrile (3f)

The compound was synthesized following the representative procedure using 4-cyanobenzaldehyde **1f** (0.131 g, 1.0 mmol), indole **2a** (0.234 g, 2.0 mmol), (NH₄)₂Fe(SO₄)₂.6H₂O (0.027 g, 7.0 mole %), and H₂O (5 mL). Yield: 329 mg (95%) as pink colored solid compound. Chemical Formula: C₂₄H₁₇N₃; Molecular Weight: 347.4119; M. P.: 209-210°C (Lit. [29] 211°C); IR (cm⁻¹): 3396, 3165, 2940, 2253, 1602, 1407, 757; ¹H NMR (400 MHz, CDCl₃): 7.96 (br s, 2H, NH), 7.56 (d, J = 8.2 Hz, 2H, Ar–H), 7.44 (d, J = 8.2 Hz, 2H, Ar– H), 7.1–7.5 (m, 8H, Ar–H), 6.63 (s, 2H, C2H), 5.92 (s, 1H, C10H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 149.7 (C11), 136.7 (C8), 132.2 (C13), 129.5 (C12), 126.7 (C9), 123.7 (C2), 122.3 (C6), 119.6 (C5), 119.5 (C4), 119.2 (C3), 118.2 (CN), 111.2 (C7), 110.0 (C14), 40.4 (C10) ppm.

3.3.7. Synthesis of 3,3'-((2-chlorophenyl)methylene)bis(1H-indole) (3g)

The compound was synthesized following the representative procedure using 2-chlorobenzaldehyde **1g** (0.140 g, 1.0 mmol), indole **2a** (0.234 g, 2.0 mmol), (NH₄)₂Fe(SO₄)₂.6H₂O (0.027 g, 7.0 mole %), and H₂O (5 mL). Yield: 323.9 mg (91%) as pink colored solid compound. Chemical Formula: $C_{23}H_{17}CIN_2$; Molecular Weight: 356.8475; M. P.: 72-73°C (Lit. [25] 74-76°C); IR (cm⁻¹): 3413, 3057, 2924, 1618, 1456, 1337, 1216, 1093, 1038, 743, 599; ¹H NMR (400 MHz, CDCl₃): δ 7.84 (br s, 2H, NH), 7.36-7.28 (m, 5H), 7.16-7.01 (m, 5H), 6.94 (t, *J* = 6.8 Hz, 2H), 6.57 (s, 2H, C2H), 6.27 (s, 1H, C10H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 141.3 (C11), 136.7 (C8), 133.9 (C12), 130.3 (C16), 129.4 (C13), 127.5 (C9), 127.0 (C14), 126.6 (C15), 123.7 (C2), 122.0 (C6), 119.8 (C5), 119.3 (C4), 118.3 (C3), 111.0 (C7), 36.6 (C10) ppm.

3.3.8. Synthesis of 3,3'-((2-methoxyphenyl)methylene) bis(1H-indole) (3h)

The compound was synthesized following the representative procedure using 2-methoxybenzaldehyde **1h** (0.136 g, 1.0 mmol), indole 2a (0.234 g, 2.0 mmol), (NH₄)₂Fe(SO₄)₂.6H₂O (0.027 g, 7.0 mole %), and H₂O (5 mL). Yield: 299 mg (85%) as white solid compound. Chemical Formula: C₂₄H₂₀N₂O; Molecular Weight: 352.4284; M. P.: 136-138°C (Lit. [30] 134-136°C); IR (cm⁻¹): 3414, 3057, 2933, 1597, 1489, 1456, 1338, 1243, 1092, 1028, 743, 600; ¹H NMR (400 MHz, CDCl₃): δ 7.83 (br s, 2H, NH), 7.39 (d, J = 8.4Hz, 2H), 7.32 (d, J = 7.6 Hz, 2H), 7.15-7.11 (m, 4H), 6.97 (t, J = 6.8 Hz, 2H), 6.92 (d, J = 8.4 Hz, 1H), 6.79 (t, J = 8.0 Hz, 1H), 6.63 (s, 2H, C2H), 6.34 (s, 1H, C10H), 3.80 (s, 3H, OCH₃) ppm; 13 C NMR (100 MHz, CDCl₃): δ 156.9 (C12), 136.7 (C8), 132.3 (C16), 129.7 (C9), 127.2 (C14), 127.1 (C11), 123.5 (C2), 121.7 (C6), 120.4 (C15), 120.0 (C5), 119.6 (C4), 119.0 (C13), 110.9 (C3), 110.6 (C7), 55.7 (OCH₃), 32.0 (C10) ppm.

3.3.9. Synthesis of 2-(di(1H-indol-3-yl)methyl)phenol (3i)

The compound was synthesized following the representative procedure using 2-hydroxybenzaldehyde 1i (0.122 g, 1.0 mmol), indole 2a (0.234 g, 2.0 mmol), (NH₄)₂Fe(SO₄)₂.6H₂O (0.027 g, 7.0 mole %), and H₂O (5 mL). Yield: 304 mg (90%) as pink colored solid compound. Chemical Formula: C₂₃H₁₈N₂O; Molecular Weight: 338.4018; M. P.: 340-342°C (Lit. [31] 341-343°C); IR (cm⁻¹): 3818, 3749, 3494, 2931, 2360, 1743, 1365, 1326, 748; ¹H NMR (250 MHz, DMSOd₆): δ 10.75 (s, 2H, NH), 9.42 (s, 1H, OH), 7.27-7.36 (m, 4H, Ar-H), 6.96-7.09 (m, 4H, Ar-H), 6.85 (t, 3H, J = 7.2 Hz, Ar-H), 6.75 (s, 2H, C2H) 6.65 (t, 1H, J = 7.0 Hz, Ar-H), 6.21 (s, 1H, C10H) ppm; ¹³CNMR (62.5 MHz, DMSO-d₆): δ 154.2 (C12), 136.5 (C8), 130.8 (C16), 129.3 (C9), 126.8 (C14), 126.5 (C11), 123.4 (C2), 120.7 (C6), 118.9 (C15), 118.5 (C5), 118.0 (C4), 117.9 (C13), 114.9 (C3), 111.3 (C7), 31.4 (C10) ppm.

3.3.10. Synthesis of 4-bromo-2-(di(1H-indol-3-yl)methyl) phenol (3j)

The compound was synthesized following the representative procedure using 2-hydroxy-5-bromobenzaldehyde **1j** (199.9 g, 1.0 mmol), indole **2a** (0.234 g, 2.0 mmol), (NH₄)₂Fe(SO₄)₂.6H₂O (0.027 g, 7.0 mole %), and H₂O (5 mL). Yield: 386 mg (93%) as pink colored solid compound. Chemical Formula: C₂₃H₁₇BrN₂O; Molecular Weight: 417.2979; M.P.: 137-139°C (Lit. [32] 136-138°C); ¹H NMR (400 MHz, CDCl₃): 10.81 (s, 1H, OH), 9.80 (brs, 2H, NH), 7.35-6.76 (m, 11H, Ar-H), 6.13 (s, 2H, C2H), 5.72 (s, 1H, C10H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 153.7 (C12), 136.8 (C8), 132.4 (C16), 131.6 (C9), 130.8 (C11), 126.6 (C13), 123.67 (C2), 122.4 (C6), 119.6 (C5), 118.4 (C4), 116.5 (C14), 115.6 (C15), 112.9 (C3), 111.3 (C7), 60.5 (C10) ppm.

3.3.11. Synthesis of 3,3'-(phenylmethylene)bis(2-methyl-1H-indole) (3k)

The compound was synthesized following the representative procedure using benzaldehyde 1k (0.106 g, 1.0 mmol), 2-methylindole **2b** (0.262 g, 2.0 mmol), (NH₄)₂Fe(SO₄)₂.6H₂O (0.027 g, 7.0 mole %), and H₂O (5 mL). Yield: 318 mg (91%) as pink colored solid compound. Chemical Formula: C₂₅H₂₂N₂; Molecular Weight: 350.4556; M.P.: 246-248°C (Lit. [25] 247-248°C); IR (cm⁻¹): 3393, 3050, 1458, 1298, 1220, 747; ¹H NMR (400 MHz, DMSO-d₆): δ 10.74 (s, 2H, NH), 7.24-7.18 (m, 7H, Ar-H), 6.88 (t, *J* = 7.5 Hz, 2H, Ar-H), 6.80 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.67 (t, *J* = 7.5 Hz, 2H, Ar-H), 5.92 (s, 1H, C10H), 2.06 (s, 6H, 2xCH₃) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ 144.7 (C11), 135.5 (C8), 132.5 (C2), 129.2 (C12), 128.7 (C13), 128.4 (C9), 126.2 (C14), 120.0 (C6), 118.9 (C5), 118.4 (C4), 117.9 112.6 (C3), 110.8 (C7), 39.1 (C10), 12.4 (CH₃) ppm.

3.3.12. Synthesis of 4-(bis(2-methyl-1H-indol-3-yl)methyl) phenol (3l)

The compound was synthesized following the representative procedure using 4-hydroxybenzaldehyde 11 (0.122 g, 1.0 mmol), 2-methylindole 2b (0.262 g, 2.0 mmol), (NH₄)₂Fe(SO₄)₂.6H₂O (0.027 g, 7.0 mole %), and H₂O (5 mL). Yield: 336 mg (92%) as pink colored solid compound. Chemical Formula: $C_{25}H_{22}N_2O$; Molecular Weight: 366.4550; M. P.: 236-238°C (Lit. [26] 238-240°C); IR (cm⁻¹): 3425, 3058, 2971, 1456, 1335, 1225, 1097, 745; ¹H NMR (400 MHz, CDCl₃): δ 9.63 (s, 2H, NH), 8.61 (s, 1H, OH), 7.15 (d, 2H, J = 7.7 Hz), 7.01 (d, 2H, J = 7.6 Hz), 6.73 (m, 4H), 6.51 (m, 4H), 5.64 (s, 1H, C10H), 1.83 (s, 6H, 2xCH₃) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 155.2 (C14), 135.1 (C8), 134.5 (C2), 131.8 (C11), 129.7 (C12), 128.5 (C9), 119.7 (C6), 118.8 (C5), 118.1 (C4), 114.8 (C13), 113.1 (C3), 110.2 (C7), 38.1 (C10), 12.3 (CH₃) ppm.

3.3.13. Synthesis of 3,3'-((4-methoxyphenyl)methylene) bis(2-methyl-1H-indole) (3m)

The compound was synthesized following the representative procedure using 4-methoxybenzaldehyde 1m (0.136 g, 1.0 mmol), 2-methylindole 2b (0.262 g, 2.0 mmol), (NH₄)₂Fe(SO₄)₂.6H₂O (0.027 g, 7.0 mole %), and H₂O (5 mL). Yield: 353 mg (93%) as pink colored solid compound. Chemical Formula: C₂₆H₂₄N₂O; Molecular Weight: 380.4816; M. P.: 146-148°C (Lit. [33] 147-150°C); IR (cm⁻¹): 3396, 3050, 1508, 1458, 1243, 745; ¹H NMR (400 MHz, CDCl₃): δ 7.71 (s, 2H, NH), 7.24 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.19 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.06 (dd, *J* = 8.0, 1.8 Hz, 2H, Ar-H), 7.02 (dd, J = 8.0 and 1.8 Hz, 2H, Ar-H), 6.87 (dt, J = 1.8 and 8.0 Hz, 2H, Ar-H), 6.81 (dt, J = 1.8 and 8.4 Hz, 2H, Ar-H), 5.96 (s, 1H, C10H), 3.80 (s, 3H, OCH₃), 2.06 (s, 6H, 2xCH₃) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 157.8 (C14), 135.9 (C8), 135.0 (C2), 131.7 (C11), 129.9 (C12), 129.0 (C9), 120.6 (C6), 119.4 (C5), 119.0 (C4), 113.7 (C13), 113.4 (C3), 109.9 (C7), 62.2 (OCH₃), 38.4 (C10), 12.4 (CH₃) ppm.

3.3.14. Synthesis of 3,3'-((4-chlorophenyl)methylene)bis(2methyl-1H-indole) (3n)

This compound was synthesized following the above mentioned general procedure using 4-chlorobenzaldehyde (0.140 g, 1.0 mmol), 2-methylindole (0.262 g, 2.0 mmol), (NH₄)₂Fe(SO₄)₂.6H₂O (0.027 g, 7.0 mole %), and H₂O (5 mL). Yield: 336 mg (92%) as faint pink colored solid compound; Chemical Formula: $C_{25}H_{21}ClN_2$; Molecular Weight:

384.9006; M. P.: 240-242°C (Lit. [34] 241-243°C); IR (cm⁻¹): 3384, 3050, 1486, 1457, 1429, 1015, 747; ¹H NMR (400 MHz, CDCl₃): δ 7.75 (s, 2H, NH), 7.24-7.21 (m, 6H, Ar-H), 7.08-7.04 (m, 2H, Ar-H), 6.98 (d, J = 8.0 Hz, 2H, Ar-H), 6.90-6.86 (m, 2H, Ar-H), 5.96 (s, 1H, C10H), 2.07 (s, 6H, 2xCH₃) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 142.8 (C11), 135.0 (C8), 131.8 (C14), 131.6 (C2), 130.4 (C12), 128.7 (C13), 128.2 (C9), 120.7 (C6), 119.2 (C5), 118.7 (C4), 112.8 (C3), 110.0 (C7), 38.6 (C10), 12.4 (CH₃) ppm.

CONCLUSION

In this study, we have developed a straightforward and facile approach for the synthesis of discrete symmetrical BIMs in a water medium. In view of this, the catalytic performance of more accessible Mohr's salt highlighting its potential for the synthesis of imperative biologically pertinent BIMs scaffolds in medicinal chemistry.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

REFERENCES

- Singh, T.P.; Singh, O.M. Mini-Reviews. Med. Chem., 2017, 18(1), 9-25.
- [2] Sharma, V.; Kumar, P.; Pathaka, D. J. Heterocycl. Chem., 2010, 47(3), 491-502.
- [3] Segraves, N.L.; Crews, P. J. Nat. Prod., 2005, 68(10), 1484-1488.
- [4] Praveen, P.J.; Parameswaran, P.S.; Majik, M.S. Synthesis, 2015, 47(13), 1827-1837.
- [5] Blunt, J.W.; Carroll, A.R.; Copp, B.R.; Davis, R.A.; Keyzers, R.A.; Prinsep, M.R. *Nat. Prod. Rep.*, **2018**, *35*(1), 8-53.
- [6] Fahy, E.; Potts, B.C.M.; Faulkner, D.J.; Smith, K. J. Nat. Prod., 1991, 54(2), 564-569.
- Bell, R.; Carmeli, S.; Sar, N. Vibrindole A. J. Nat. Prod., 1994, 57(11), 1587-1590.
- [8] Bifulco, G.; Bruno, I.; Riccio, R.; Lavayre, J.; Bourdy, G. J. Nat. Prod., 1995, 58(8), 1254-1260.
- [9] Oh, K.B.; Mar, W.; Kim, S.; Kim, J.Y.; Lee, T.H.; Kim, J.G.; Shin, D.; Sim, C.J. Shin. J. Biol. Pharm. Bull., 2006, 29(3), 570-573.
- [10] Porter, J.K.; Bacon, C.W.; Robbins, J.D.; Himmelsbach, D.S.; Higman, H.C. J. Agric. Food Chem., 1976, 25(1), 88-93.
- [11] Khuzhaev, B.U.; Aripova, S.F.; Shakirov, R.S. Chem. Nat. Compd., 1994, 30(5), 635-636.
- [12] Garbe, T.R.; Kobayashi, M.; Shimizu, N.; Takesue, N.; Ozawa, M.; Yukawa, H. J. Nat. Prod., 2000, 63(5), 596-598.
- [13] Imran, S.; Taha, M.; Ismail, N.H. Curr. Med. Chem., 2015, 22(38), 4412-4433.

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- [14] Shiri, M.; Zolfigol, M.A.; Kruger, H.G.; Tanbakouchian, Z. Chem. Rev., 2010, 110(4), 2250-2293.
- [15] Hikawa, H.; Yokoyama, Y. *RSC Advances*, **2013**, *3*(4), 1061-1064.
- [16] Abe, T.; Nakamura, S.; Yanada, R.; Choshi, T.; Hibino, S.; Ishikura, M. Org. Lett., 2013, 15(14), 3622-3625.
- [17] Brahmachari, G.; Banerjee, B. ACS Sustain. Chem. & Eng., 2014, 2(12), 2802-2812.
- [18] Huo, C.; Wang, C.; Sun, C.; Jia, X.; Wang, X.; Chang, W.; Wu, M. Adv. Synth. Catal., 2013, 355(10), 1911-1916.
- [19] Lucarini, S.; Mari, M.; Piersanti, G.; Spadoni, G. RSC Advances, 2013, 3(41), 19135.
- [20] Zhuo, M.H.; Jiang, Y.J.; Fan, Y.S.; Gao, Y.; Liu, S.; Zhang, S. Org. Lett., 2014, 16(4), 1096-1099.
- [21] Mendes, S.R.; Thurow, S.; Penteado, F.; da Silva, M.S.; Gariani, R.A.; Perin, G.; Lenardão, E.J. *Green Chem.*, **2015**, *17*(8), 4334-4339.
- [22] Lin, L.P.; Yuan, P.; Jiang, N.; Mei, Y.N.; Zhang, W.J.; Wu, H.M.; Zhang, A.H.; Cao, J.M.; Xiong, Z.X.; Lu, Y.; Tan, R.X. Org. Lett., 2015, 17(11), 2610-2613.
- [23] Mo, L.P.; Ma, Z.C.; Zhang, Z.H. Synth. Commun., 2005, 35(15), 1997-2004.
- [24] Silveira, C.C.; Mendes, S.R.; Líbero, F.M.; Lenardão, E.J.; Perin, G. *Tetrahedron Lett.*, **2009**, *50*(44), 6060-6063.

- [25] Hasaninejad, A.; Zare, A.; Sharghi, H.; Arkivoc, K.N. -; 2007, U. ARKIVOC, 2007, 14, 39.
- [26] Firouzabadi, H.; Iranpoor, N.; Jafari, A.A. J. Mol. Catal. Chem., 2006, 244(1-2), 168-172.
- [27] Deb, M.L.; Bhuyan, P.J. Tetrahedron Lett., 2006, 47(9), 1441-1443.
- [28] Wang, L.; Han, J.; Tian, H.; Sheng, J.; Fan, Z.; Tang, X. Synlett., 2005, 2, 337-339.
- [29] Bandgar, B.P.; Bettigeri, S.V.; Joshi, N.S. Monatsh. Chem., 2004, 135(10), 1265-1273.
- [30] Ghorbani-Vaghei, R.; Veisi, H.; Keypour, H.; Dehghani-Firouzabadi, A.A. Mol. Divers., 2010, 14(1), 87-96.
- [31] Zhang, Z.H.; Yin, L.; Wang, Y.M. Synthesis (Stuttg), 2005, 12, 1949-1954.
- [32] Naidu, K.R.M.; Khalivulla, S.I.; Kumar, P.C.R.; Lasekan, O. Org. Commun., 2012, 5(3), 150-159.
- [33] Zhang, S.; Fan, W.; Qu, H.; Xiao, C.; Wang, N.; Shu, L.; Hu, Q.; Liu, L. Curr. Org. Chem., 2012, 16(7), 942-948.
- [34] Azizi, N.; Gholibeghlo, E. Manocheri. Z. Sci. Iran., 2012, 19(3), 574-578.
- [35] Happened, W. Chemistry of the Elements; Butterworth-Heinemann, E., Ed.; 1997, Vol. 25, pp. 1070-1112.