

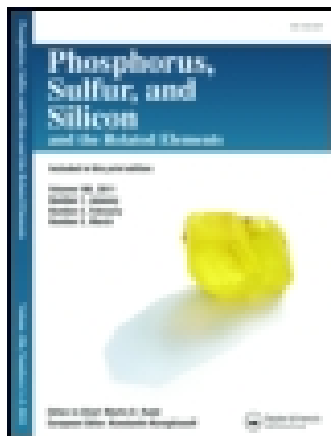
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Green Protocol for the Synthesis of Bisindolymethanes and Evaluation of Their Antimicrobial Activities

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Green Protocol for the Synthesis of Bisindolylmethanes and Evaluation of Their Antimicrobial Activities

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A simple, efficient, and ecofriendly procedure for the preparation of bis(indolyl)methanes via electrophilic substitution reactions of 2-phenylindoles with aldehydes is described. The reaction takes place in the presence of glacial acetic acid and a catalytic amount of anhydrous ferric chloride. All the synthesized compounds have been characterized by elemental analysis and spectral data (IR and ¹H NMR). They have also been evaluated for their antibacterial and antifungal activities, and some of them have shown promising results against S. aureus, E. coli, A. flavus, and A. niger.

Keywords Anhydrous ferric chloride; bis(indolyl)methanes; ecofriendly procedure; electrophilic substitution reaction; green chemistry techniques; 2-phenylindole

INTRODUCTION

The indole nucleus is associated with a wide spectrum of biological activities. The introduction of a phenyl group at the 2-position of the indole ring enhances biological activities such as monoamine oxidase inhibition,^{1,2} electrochemical behavior,³ mammary tumor inhibiting activity, and estrogenic and anti-estrogenic properties.⁴ As such, bisindolylalkanes and their derivatives constitute an important group of bioactive metabolites of terrestrial and marine origin⁵ and are useful for drug design.⁶ Bisindolylmethanes are the most active cruciferous substances for promoting beneficial estrogen metabolism and inducing

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Dedicated to the late Prof. Vijai N. Pathak.

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apoptosis in human cancer cells.⁷ They have also shown potent CNS depressant activities, tranquilizing effects, and neuroplegic activities.^{8,9} Therefore, there is a great deal of interest in the synthesis of these compounds. Various methods are available in the literature^{10–21} for the synthesis of bisindolylmethanes, but there are only scant reports on the ecofriendly synthesis of bisindoles of 2-phenylindoles. In continuation to our earlier work on various 2-phenylindoles,²² we prepared some bisindolylmethane derivatives by improved green chemistry techniques. As a part of this program, we wish to report various strategies for the synthesis of 2,2'-diaryl-3,3'-alkylidene/arylidene bisindoles and to assess the efficiency of these synthetic routes and make a comparative study. We have used various green chemistry techniques, viz., microwave, grindstone chemistry, and ultrasonication for this synthesis. Glacial acetic acid and inexpensive catalysts such as anhydrous ferric chloride (anhyd. FeCl_3) are used to obtain these target molecules.

RESULTS AND DISCUSSION

A series of 2,2'-diaryl-3,3'-alkylidene/arylidene bisindoles have been synthesized using new, improved green chemistry techniques. These compounds are stable and contain the indole and appropriate aldehyde in a 2:1 ratio (Table I).

2-Arylindoles are prepared by the method of Joshi et al.²³ 2-Arylindole (20 mmol) reacts with the appropriate aldehyde (10 mmol) in the presence of (a) glacial acetic acid or (b) a catalytic amount of anhydrous ferric chloride (anhy. FeCl_3) by employing various green chemistry techniques to give the desirable title compounds. The results obtained are presented in Table II.

The results reveal that microwave-assisted reactions take place in the shortest time period (using anhy. FeCl_3) and give highest yield (using glacial acetic acid) of the title compounds. The synthetic steps are illustrated in Scheme 1.

In the IR spectra of title compounds (**2a–e**), the $>\text{NH}$ absorption band appears at $3464\text{--}3342\text{ cm}^{-1}$ and the aromatic C–H stretching absorption peak appears at 3050 cm^{-1} . The aliphatic C–H stretching vibration is observed at $2850\text{--}2836\text{ cm}^{-1}$ and the aromatic $>\text{C}=\text{C}<$ absorption band is observed at 1679 cm^{-1} . An absorption band due to C–Br appears at 550 cm^{-1} .

The ^1H NMR spectra of 2-arylindole revealed the presence of a broad resonance signal in the region of δ 8.0–8.6 ppm, which is attributed to $>\text{N–H}$ proton, and the methine proton signal ($=\text{CH}$, at C-3) appears

TABLE I The Physical and Analytical Data of 2,2'-Diaryl-3,3'-alkylidene/arylidene Bisindoles (2a-e)

Compd. No.	X	Y	Mp (°C)	Molecular Formula	C%		H%		N%	
					Found	Calcd.	Found	Calcd.	Found	Calcd.
2a	H	H	150	C ₂₉ H ₂₂ N ₂	87.40	87.43	5.51	5.52	7.01	7.03
2b	4-Br	4-FC ₆ H ₄	276	C ₃₅ H ₂₄ BrFN ₂	73.53	73.55	4.19	4.20	4.88	4.90
2c	4-Br	4- CH ₃ OC ₆ H ₄	282	C ₃₆ H ₂₇ BrN ₂ O	74.06	74.09	4.61	4.63	4.79	4.80
2d	4-F	4-FC ₆ H ₄	261	C ₃₅ H ₂₄ F ₂ N ₂	82.32	82.35	4.68	4.70	5.47	5.49
2e	4-F	4- CH ₃ OC ₆ H ₄	273	C ₃₆ H ₂₇ FN ₂ O	82.72	82.75	5.15	5.17	5.34	5.36

TABLE II Results and Conditions of the Synthesis of 2,2'-Diaryl-3,3'-alkylidene/arylidene Bisindoles (2a–e)

Compd. No.	Yield (%)						Time required (min.)					
	(a)			(b)*			(a)			(b)		
	(i)	(ii)	(iii)	(i)	(ii)	(iii)	(i)	(ii)	(iii)	(i)	(ii)	(iii)
2a	84	83	75	77	75	69	7	10	80	4	10	60
2b	82	78	73	74	70	67	7	20	70	5	20	60
2c	86	83	76	78	73	71	5	15	50	3.5	10	50
2d	85	79	73	81	76	70	6	10	80	4.5	10	70
2e	83	77	72	77	75	66	6	20	60	4	10	40

*Isolated yield.

(a) = using glacial CH_3COOH .

(b) = using anhy. FeCl_3 .

(i) = by microwave irradiation.

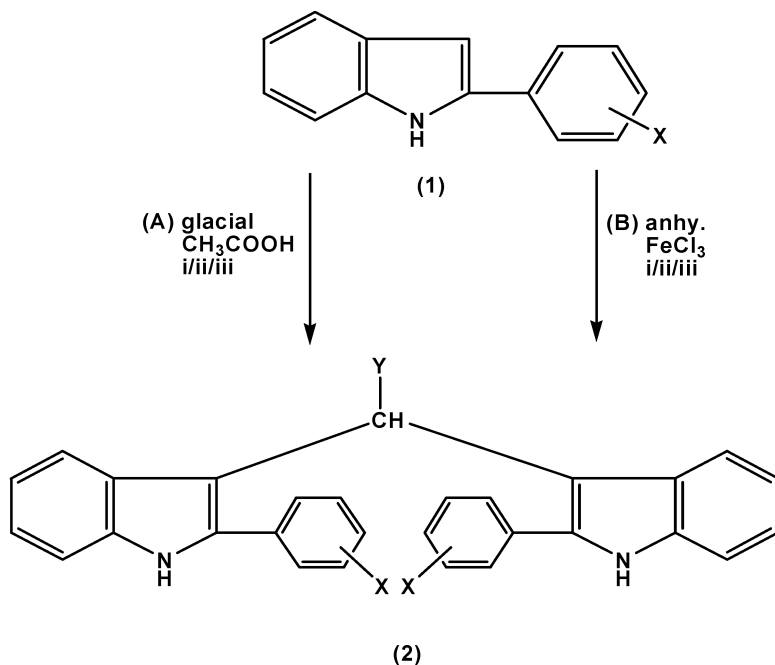
(ii) = by grinding.

(iii) = by ultrasound irradiation.

as a sharp singlet at δ 6.7–6.9 ppm. In the ^1H NMR spectra of title compounds (**2a–e**), the disappearance of the resonance signal due to a methine proton at C-3 position shows the formation of bisindoles. Compound (**2a**) shows additional resonance signals at δ 4.36–4.56 ppm as a double doublet, which is due to $>\text{CH}_2$ protons. In compounds (**2b–e**), the appearance of a sharp singlet at δ 5.5–6.0 ppm due to the arylidene $-\text{CH}$ proton also supports the bisindole formation. The aromatic and $>\text{N}-\text{H}$ resonance signals remain unaltered. The IR and ^1H NMR data of all synthesized compounds are presented in Table III.

EXPERIMENTAL

All the melting points were determined in open glass capillary tubes and are uncorrected. The IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin Elmer 557 grating infrared spectrophotometer as KBr pellets. ^1H NMR spectra were recorded on a Bruker spectrophotometer (300 MHz) using CDCl_3 as a solvent. TMS was used as internal standard (chemical shift in δ , ppm). The microwave-assisted reactions were carried out in a domestic MW oven (LG MS–194A) operating at 800 W, and ultrasound irradiation reactions were carried out in an ultrasonic bath (Toshniwal–SW-4) operating at 150 W generating 37 KHz output frequency. The purity of the compounds was checked by TLC using silica gel-G as adsorbent, UV light or iodine accomplished visualization.



X = H, 4 - Br, 4 - F

Y = C₆H₄F, C₆H₄OCH₃

- (i) Microwave irradiation
- (ii) Grinding/rt
- (iii) Ultrasonication

SCHEME 1

2-Arylindoles were prepared by the method of Joshi et al.²³ Compounds 2a¹² and 2d²⁴ have been synthesized earlier by conventional methods, but we report some new routes for the synthesis of these compounds. Some 2,2'-diaryl-3,3'-alkylidene/arylidene bisindoles (2a-e) were synthesized by the following routes:

Method (i): Microwave Activation Method

(a) Using Glacial Acetic Acid

2-Aryl-1H-indole (1 mmol), the appropriate aldehyde (0.5 mmol), and glacial acetic acid (2 mL) were taken in a conical flask (100 cm³) and irradiated with microwaves for 5–7 min at 800 W. The color of

TABLE III Spectral Data of 2,2'-Diaryl-3,3'-alkylidene/arylidene Bisindoles (2a–e)

Compd. no.	IR (KBr) ν_{\max} cm^{-1}	^1H NMR (CDCl_3) δ ppm
2a	3464 (NH str.), 3050 (aromatic C–H str.), 2836 (aliphatic C–H str.), 1679 (aromatic C = C str.)	4.36–4.56 (dd, CH_2 , 2H), 6.7–7.9 (m, <i>ArH</i> , 18H), 8.0 (s, <i>NH</i> , 2H)
2b	3400 (NH str.), 3050 (aromatic C–H str.), 2840 (aliphatic C–H str.), 1679 (aromatic C = C str.), 550 (C–Br), 1236 (C–F)	5.5 (s, <i>CH</i> , 1H), 6.8–7.7 (m, <i>ArH</i> , 21H), 8.0 (s, <i>NH</i> , 2H)
2c	3386 (NH str.), 3050 (aromatic C–H str.), 2836 (aliphatic C–H str.), 1679 (aromatic C = C str.), 550 (C–Br), 1158 (C–O–C)	6.0 (s, <i>CH</i> , 1H), 3.8 (s, OCH_3 , 3H), 6.7–7.3 (m, <i>ArH</i> , 21H), 8.0 (s, <i>NH</i> , 2H).
2d	3400 (NH str.), 3050 (aromatic C–H str.), 2850 (aliphatic C–H str.), 1679 (aromatic C = C str.), 1229 (C–F)	5.5 (s, <i>CH</i> , 1H), 6.8–7.9 (m, <i>ArH</i> , 21H), 8.0 (s, <i>NH</i> , 2H).
2e	3342 (NH str.), 3050 (aromatic C–H str.), 2836 (aliphatic C–H str.), 1679 (aromatic C = C str.), 1329 (C–F), 1136 (C–O–C)	5.5 (s, <i>CH</i> , 1H), 3.8 (s, OCH_3 , 3H), 6.5–8.0 (m, <i>ArH</i> , 21H), 8.1 (s, <i>NH</i> , 2H).

reaction mixture gradually turned from light brown to dark brown. After completion of the reaction (checked by TLC), the reaction mixture was allowed to cool to room temperature and then poured into ice cold water. It was filtered and recrystallized from benzene to afford the pure product.

(b) Using Anhydrous FeCl_3

In a conical flask (100 cm^3), a mixture of well-ground anhydrous FeCl_3 (0.2 mmol, 0.03 g) and silica gel (3g) was combined with a solution of 2-aryl-1H-indole (1 mmol) and the appropriate aldehyde (0.5 mmol) in dichloromethane (15 mL). Under reduced pressure, the mixture was dried to a powder and then irradiated with microwaves for 3.5–5 min at 235 W. The color of the mixture gradually turned from pink to maroon. After completion of the reaction (checked by TLC), the reaction mixture was allowed to cool to room temperature and extracted with diethyl ether (3 \times 15 mL) followed by washing with water (3 \times 15 mL). The ether layer was dried over anhydrous magnesium sulfate and then evaporated to afford the crude compound. The crude compound

was purified by silica gel column chromatography using benzene:ethyl acetate (80:20) as eluent to afford the pure title compound.

Method (ii): Grindstone Method

(a) Using Glacial Acetic Acid

2-Aryl-1H-indole (1 mmol), the appropriate aldehyde (0.5 mmol), and glacial acetic acid (2 mL) were taken in a mortar and ground using a pestle for 10–20 min to give a dark brown colored mixture. After completion of the reaction (checked by TLC), the reaction mixture was poured into ice cold water, filtered, washed well, and recrystallized from benzene to afford the pure compound.

(b) Using Anhydrous $FeCl_3$

The mixture of 2-aryl-1H-indole (1 mmol) and the appropriate aldehyde (0.5 mmol) were taken in a mortar, then anhy. $FeCl_3$ (0.2 mmol, 0.03g) was added to it and ground well using a pestle for 10–20 min to give a dark brown colored semi-viscous substance. After completion of the reaction (checked by TLC), the reaction mixture was extracted with diethyl ether (3×15 mL) followed by washing with water (3×15 mL). The ether layer was dried over anhy. magnesium sulfate and then evaporated to afford the crude compound, which was purified by silica gel column chromatography to afford the pure title compound.

Method (iii): Ultrasonic Irradiation Method

(a) Using Glacial Acetic Acid

A solution of 2-aryl-1H-indole (1 mmol) in benzene (10 mL), the appropriate aldehyde (0.5 mmol) in benzene (5 mL), and glacial acetic acid were taken in a conical flask (100 cm^3) and irradiated with ultrasonic waves for 50–80 min at $40\text{ }^\circ\text{C}$. After completion of the reaction (checked by TLC), the reaction solution was extracted with benzene (3×15 mL) followed by washing with water (3×15 mL). The benzene layer was dried over anhy. magnesium sulfate. After removal of the benzene layer, we obtained the pure title compound.

(b) Using Anhydrous $FeCl_3$

A solution of 2-aryl-1H-indole (1 mmol) in benzene (10 mL), the appropriate aldehyde (0.5 mmol) in benzene (5 mL), and anhy. $FeCl_3$ (0.2 mmol, 0.03 g) were taken in a conical flask (100 cm^3) and irradiated with ultrasonic waves for 40–70 min at $40\text{ }^\circ\text{C}$. After completion of the reaction, as indicated by TLC, the reaction solution was extracted with benzene (3×15 mL) followed by washing with water (3×15

TABLE IV Antibacterial Activity of 2,2'-Diaryl-3,3'-alkylidene/arylidene Bisindoles (2a-e)

Compd. No.	Mean Value of Area of inhibition in mm (1000 ppm) IZ (AI)		Mean Value of Area of inhibition in mm (800 ppm) IZ (AI)		Mean Value of Area of inhibition in mm (400 ppm) IZ (AI)		Mean Value of Area of inhibition in mm (200 ppm) IZ (AI)	
	<i>S. aureus</i>	<i>E. coli</i>	<i>S. aureus</i>	<i>E. coli</i>	<i>S. aureus</i>	<i>E. coli</i>	<i>S. aureus</i>	<i>E. coli</i>
Streptomycin	12	8.8	10.4	6	9.4	4.2	8	3
2a	9.0(0.75)	6.5(0.73)	9.0(0.86)	5.3(0.88)	7.1(0.75)	2.0(0.47)	5.8(0.72)	1.7(0.56)
2b	10.2(0.85)	7.0(0.79)	7.6(0.73)	4.1(0.68)	7.3(0.77)	2.7(0.64)	6.3(0.78)	2.3(0.76)
2c	12.5(1.04)	9.4(1.06)	11.0(1.05)	7.0(1.16)	9.4(1.00)	5.0(1.19)	9.6(1.20)	3.7(1.23)
2d	11.8(0.98)	7.5(0.85)	9.8(0.94)	4.0(0.66)	9.0(0.95)	3.1(0.73)	8.0(1.00)	2.0(0.66)
2e	12.2(1.01)	9.0(1.02)	10.4(1.00)	6.6(1.10)	10.0(1.06)	4.4(1.04)	9.6(1.20)	3.2(1.06)

IZ = Inhibition area (zone) excluding diameter of disc.

AI (Activity Index) = Inhibition area of sample/inhibition area of standard.

TABLE V Antifungal Activity of 2,2'-Diaryl-3,3'-alkylidene/arylidene Bisindoles (2a-e)

Compd. No.	Mean Value of Area of inhibition in mm (1000 ppm) IZ (AI)		Mean Value of Area of inhibition in mm (800 ppm) IZ (AI)		Mean Value of Area of inhibition in mm (400 ppm) IZ (AI)		Mean Value of Area of inhibition in mm (200 ppm) IZ (AI)	
	<i>A. flavus</i>	<i>A. niger</i>	<i>A. flavus</i>	<i>A. niger</i>	<i>A. flavus</i>	<i>A. niger</i>	<i>A. flavus</i>	<i>A. niger</i>
Mycostatin	10.2	11	9	10.4	7.2	8	5	6.6
2a	9.5(0.93)	10.0(0.90)	7.0(0.77)	8.3(0.79)	5.5(0.76)	6.8(0.85)	3.0(0.60)	5.3(0.80)
2b	8.0(0.78)	8.9(0.80)	7.6(0.84)	8.0(0.76)	5.0(0.69)	7.0(0.87)	3.8(0.76)	4.0(0.60)
2c	11.0(1.07)	11.5(1.04)	10.0(1.11)	10.8(1.03)	8.3(1.15)	9.2(1.15)	5.0(1.00)	7.1(1.07)
2d	7.6(0.74)	8.0(0.72)	7.4(0.82)	8.0(0.76)	6.0(0.83)	6.8(0.85)	3.0(0.60)	5.3(0.80)
2e	10.7(1.04)	11.0(1.00)	10.1(1.12)	11.0(1.05)	7.9(1.09)	8.7(1.08)	5.6(1.12)	6.9(1.04)

IZ = Inhibition area (zone) excluding diameter of disc.

AI (Activity Index) = Inhibition area of sample/inhibition area of standard.

mL). The benzene layer was dried over anhydrous magnesium sulfate. The benzene layer was removed in vacuo to afford the crude compound, which was purified by silica gel column chromatography using benzene/ethylacetate as the eluent to afford the desired compound. The characteristic and analytical data of these compounds are given in Table I. The comparative data of various procedures are tabulated in Table II.

Antibacterial and Antifungal Activities of 2,2'-Diaryl-3,3'-alkylidene/arylidene Bisindoles (2a–e)

All the synthesized title compounds were screened for their antibacterial activity against Gram-positive bacteria *S. aureus* and Gram-negative bacteria *Escherichia coli* at different concentrations using the inhibition zone technique²⁵ (Table IV). All the synthesized title compounds were also screened for their antifungal activity against the fungi *Aspergillus flavus* and *Aspergillus niger* at different concentrations, and results obtained were recorded in Table V.

Streptomycin and mycostatin were used as reference compounds for evaluating the antibacterial and antifungal activities, respectively. Compounds **2c** and **2e** showed greater activity due to the presence of the methoxy group in the bisindole moiety. The possible use of these compounds as drugs is being explored. All other compounds showed significant antibacterial and antifungal activities at 1000, 800, 400, and 200 ppm concentrations, respectively.

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