Original Article

Three-Component Synthesis of Bis(indolyl)methane with Sulfanilic Acid as an Efficient Catalyst

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ABSTRACT

The biological activities and therapeutic qualities of indoles as well as their derivatives have garnered significant attention. I n this study, the solid acidic organocatalyst (sulfanilic acid) was examined for the synthesis of derivatives of *bis*(indolyl)methanes (BIMs) at ambient temperature and in water and ethanol as solvent. BIMs was prepared and characterized by appearance, TLC, FT-IR, and melting point and were further supported by CHNS analysis. The approach has a lot of advantages, including a clean reaction, operational simplicity, a simple experimental work-up process, waste minimization, non-toxicity, quicker reaction times, and high yields of the compounds.

Introduction

The biological activities and therapeutic qualities of indoles as well as their derivatives have garnered significant attention [1]. Certain derivatives of BIM have the ability to enhance the body's inherent hormone metabolism and stimulate the production of beneficial estrogen (2-hydroxyestrogen) [2]. In addition, certain derivatives of bis(indolyl)methanes are used as antibiotics [3] Some of BIMs possess promising biological effects for instanse cardiovascular, antipyretic, anti-fungal, anti-inflammatory, anti-convulsant, [4] anti-cancer agents [5], anti-HIV [6], anti-proliferative agents [7], antileishmanial [8], antiangiogenic [9], antihyperglycemic [10], antimetastatic [11], and exhibit various physiological properties [12]. Building Information Models (BIMs) possess a wide range of pharmacological properties, including the ability to enhance hormone synthesis inside the body via the regulation of natural metabolic processes. They significantly influence both women's and men's estrogen metabolism. They contain anti-

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carcinogenic activity and inhibit the abnormal growth of cells. They are also effective in treating fibromyalgia and cervical dysplasia [13]. 3,3-bis-(indolyl)methane has an important role in breast cancer prevention [14].

Green chemistry prioritizes the use of environmentally friendly reagents, non-toxic chemicals, and reagents in catalytic quantities. It also promotes the use of water as a sustainable solvent and the avoidance of volatile organic solvents [15].

Solid acidic substances have the capacity to substitute powerful liquid acids, hence mitigating corrosion issues linked to them and the resulting environmental risks. Solid acids have been widely used in chemical methodologies due to their significant benefits, such as their high reactivity, lack of toxicity, affordability, compatibility with the environment, operational simplicity, and ease of isolation compared to powerful liquid acids [16]. In this study, the catalytic activity of sulfanilic acid as an efficient and safe solid acidic catalyst toward the fabrication of Bis(indolyl)methanes derivatives in H_2O/ethanol and ambient temperature is describe.

Experimental

The compounds used in this study were procured from Alfa Aesar and Aldrich, and were employed without undergoing further purification. The identification of the products was accomplished by the comparison of their physical data with that of established samples or by analyzing their spectrum data. The measurement of melting points was conducted using a Buchi 510 melting point instrument, and the results obtained uncorrected. The PerkinElmer RXI spectrometer was used to record Fourier-transform infrared (FT-IR) spectra. Thin layer chromatography (TLC) analysis was used to monitor the progress of reactions using Merck pre-coated silica gel 60 F_{254} aluminum sheets, with visualization facilitated by ultraviolet (UV) light.

*General Method for the Fabrication of Bis(indolyl)methanes (**3a–3k**)*

A solution containing 1 mmol of aryl aldehydes, 2 mmol of indole derivative, and 10% mol of sulfanilic acid, together with a 5 mL combination of water and ethanol, was agitated at room temperature. Upon the conclusion of the reaction, as verified using thin-layer chromatography (TLC) analysis, the resultant precipitated product was subjected to filtration, followed by a thorough washing with distilled water. Subsequently, the product was dried to get the corresponding products with exceptional purity.

Characterization of Synthesized BIMs

3a: IR (KBr, cm^{-1}): 3399.87, 3055.06, 1610.21, 1489.61, 1301.26, 1218.23, 1010.92, and 597.93.

3b: IR (KBr, cm^{-1}): 3382.4, 3055.08, 1596.08, 1484.27, 1302.28, 1221.94, 1018.35, and 597.91.

3c: IR (KBr, cm^{-1}): 3385.98, 1610.81, 1457.67, and 1329.50.

3d: IR (KBr, cm^{-1}): 3388.75, 3056.55, 1595.74, 1459.96, 1302.86, 1271.02, 1093.60, and 596.2.

3e: IR (KBr, cm^{-1}): 3397.45, 3053.84, 1593.21, 1487.88, 1305.08, 1224.23, 1016.14, and 606.54.

3f: IR (KBr, cm^{-1}): 3379.08, 3056.53, 1559.99, 1460.34, 1305.17, 1263.61, 1016.13, and 596.32.

3g: IR (KBr, cm^{-1}): 3391.40, 1526.38, 1396.51, 1243.94, 1018.94, and 597.98.

3h: IR (KBr, cm^{-1}): 3389.75, 1615.76, 1457.3, 1302.08, 1221.93, 1013.99, and 596.22.

3i: IR (KBr, cm^{-1}): 3390.46, 1584.97, 1462.72, 1339.07, 1218.29, 1011.36, and 599.97.

3j: IR (KBr, cm^{-1}): 3393.60, 3051.58, 1608.26, 1457.72, 1299.56, 1219.33, 1015.82, and 594.12.

3k: IR (KBr, cm^{-1}): 3384.10, 3047.19, 1481.36, 1304.08, 1222.28, 1019.00, and 599.93.

Results and Discussion

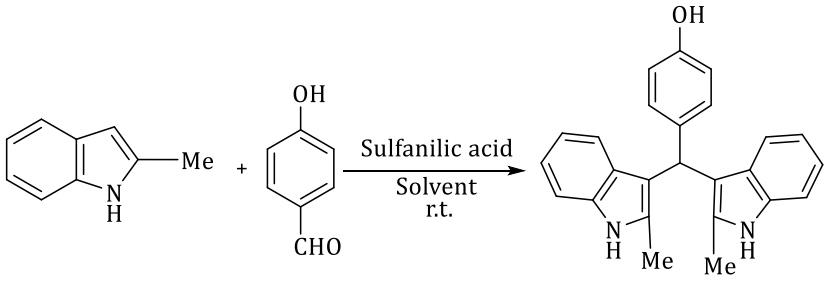
In this study, aldehydes and 2-methyl indole reacted in water/ethanol at ambient temperature in the presence of sulfanilic acid to produce bis(indolyl)methanes (**3a–3k**). To improve the reaction conditions, the reaction of 2-methylindole and 4-hydroxy benzaldehyde were used as the model reaction. Model reaction was performed at ambient temperature in a mixture of H_2O/ethanol. Optimized reaction condition is indicated in Table 1 and the desired condition was chosen that is illustrated in bold (Table 1, entry 3). Presence of catalyst is urgent for this reaction and the reaction did not occur in the absence of catalyst even after a long time (Table 1, entry 1).

A set of bis(indolyl)methanes with various substitutions were effectively synthesized, and the findings are presented in Table 2. The desired products were fabricated in satisfactory yields (**3a-3k**) (76-100 %) (Scheme 1).

Mechanism of the Reaction

The reaction mechanism was likely regulated, as depicted in Scheme 2. In the proposed mechanism, aldehydes 1 were activated and subsequently nucleophilically attacked by indoles, resulting in the formation of a 2-hydroxy(2-indo-3-lyl) derivative (B). This intermediate (B) then undergoes a nucleophilic substitution reaction with another indole molecule, leading to the production of bis(indolyl)methanes through the removal of water.

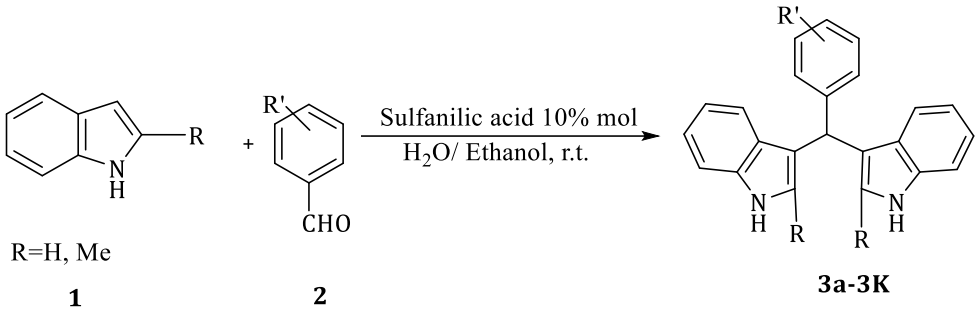
Table 1 Optimization of the reaction condition for the synthesis of **3a**



1a **2a** **3a**

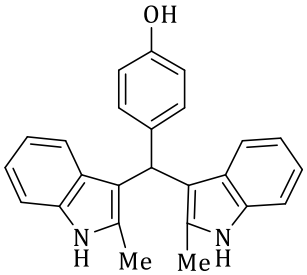
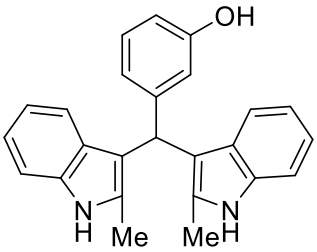
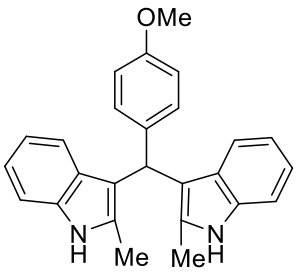
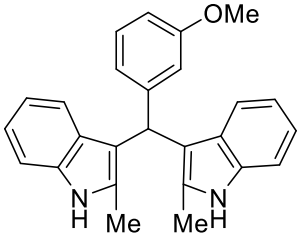
Entry	Catalyst (mol%)	Solvent	Time (min)[a]	Yield (%)[b]
1	None	H_2O-EtOH (1:1, v:v)	h	N.R.
2	5	H_2O-EtOH (1:1, v:v)	75	90
3	10	H_2O-EtOH (1:1, v:v)	60	100
4	15	H_2O-EtOH (1:1, v:v)	120	87
5	17	H_2O-EtOH (1:1, v:v)	120	70
6	20	H_2O-EtOH (1:1, v:v)	90	92
7	10	EtOH	7 h	87
8	10	*n*-hexane	7 h	87
9	10	H_2O	7 h	80
10	10	None	7 h	trace

Reaction was performed with 2-methylindole **1a** (2 mmol), 4-hydroxy benzaldehyde **2a** (1 mmol), solvent (5 mL), and catalyst at ambient temperature
[a] Reaction progress was monitored with TLC
[b] Isolated yield



Scheme 1 Synthesis of the bis-indolyl methane derivatives

Table 2. Sulfanilic acid catalyzed synthesis of *bis*-indolyl methane derivatives

Entry	Product	Time (min)	Yield (%)[a]	Melting point (°C) Obs. (Reported) [Ref.]
2	 **3a**	60	100	222-224 (224) [17]
3	 **3b**	90	92	215-218 (220) [17]
4	 **3c**	30	86	188-190 (190) [18]
5	 **3d**	60	97	241 (240) [19]

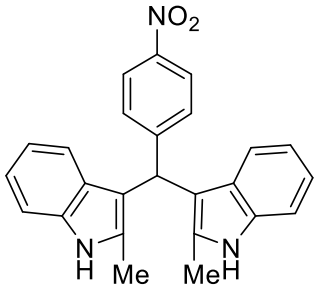
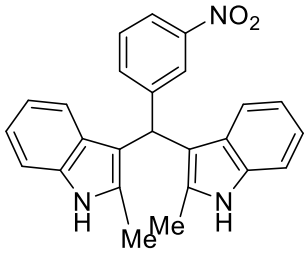
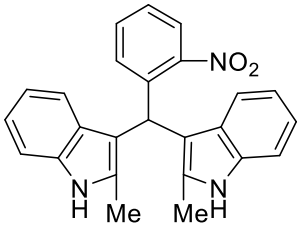
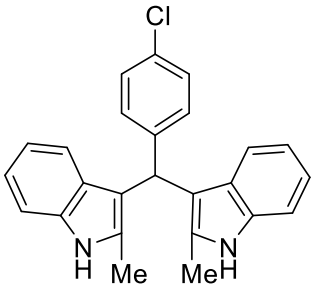
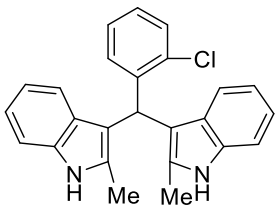
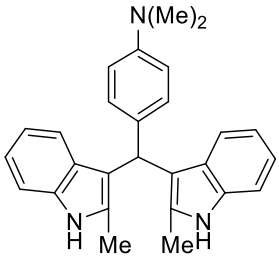
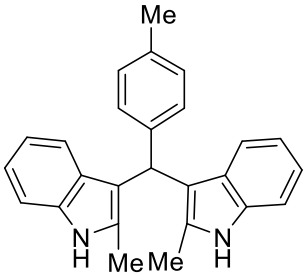
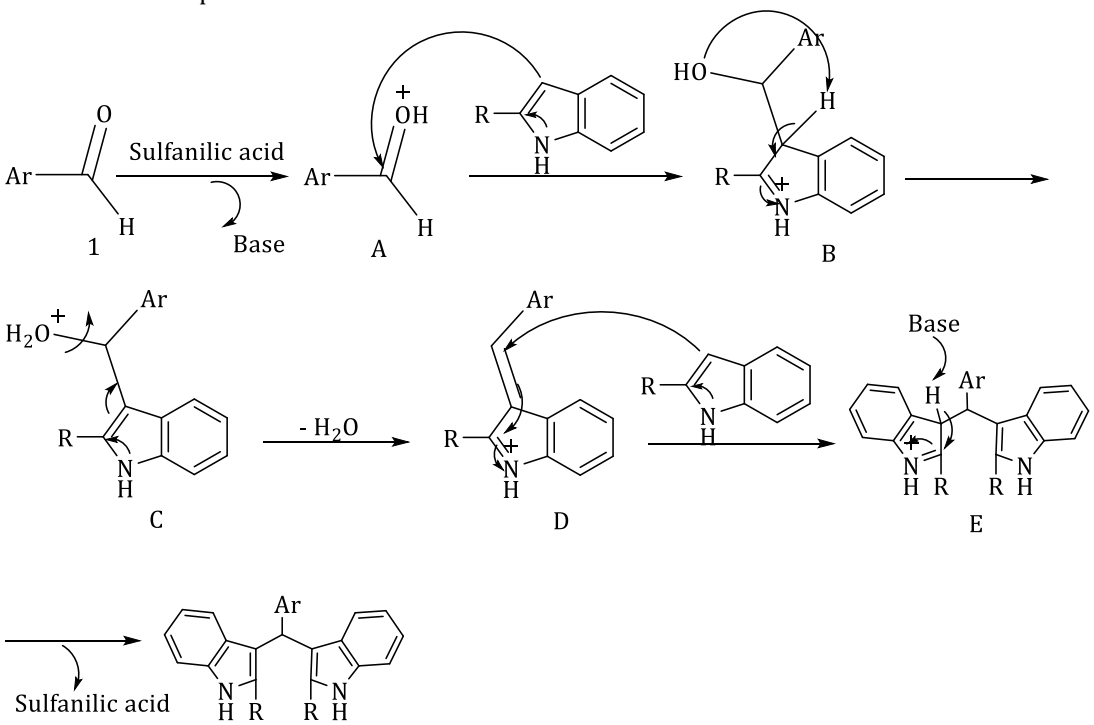
Entry	Product	Time (min)	Yield (%)[a]	Melting point (°C) Obs. (Reported) [Ref.]
6	 3e	10	98	235-237 (235-241) [19]
7	 3f	30	81	279-280 (281) [20]
8	 3g	30	80	245-247 (247) [17]
9	 3h	15	98	185-186 (186-188) [18]
10	 **3i**	60	96	225-227 (229) [19]

Table 2. Continued

Entry	Product	Time (min)	Yield (%)[a]	Melting point (°C) Obs. (Reported) [Ref.]
11	 **3j**	120	76	230-231(233) [17]
12	 **3k**	60	96	172-174 (174-175) [18]

[a] Yields refer to isolated products



Scheme 2 The suggested mechanism for the formation of BIMs (**3a-3k**) catalyzed by sulfanilic acid

Conclusion

Sulfanilic acid was used as a heterogeneous catalyst to synthesis a sequence of BIMs. The experimental approach is easy, straightforward, and capable of accommodating a wide range of substrates, resulting in a diverse array of BIMs. There is no significant influence of the functional groups in the aromatic ring of the aldehydes in the yield

percentage of the reaction products. The products were identified as bis(indolyl)methanes and have been further ascertained by Fourier transform-infrared (FT-IR) spectroscopy as well as melting point and elemental analysis.

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References

[1] Banari H., Kiyani H., Pourali A.R., Bisindolization reaction employing phthalimide-*N*-sulfonic acid as an efficient catalyst, *Current Organocatalysis*, 2020, **7**:124 [Crossref], [Google Scholar], [Publisher]

[2] Yaghoubi A., Dekamin M.G., Arefi E., Karimi B., Propylsulfonic acid-anchored isocyanurate-based periodic mesoporous organosilica (PMO-ICS-Pr-SO_3H):A new and highly efficient recoverable nanoporous catalyst for the one-pot synthesis of *bis* (indolyl) methane derivatives, *Journal of Colloid and Interface Science*, 2017, **505**:956 [Crossref], [Google Scholar], [Publisher]

[3] Kalla R.M.N., Hong S.C., Kim I., Synthesis of bis (indolyl) methanes using hyper-cross-linked polyaromatic spheres decorated with bromomethyl groups as efficient and recyclable catalysts, *ACS Omega*, 2018 **3**:2242[Crossref], [Google Scholar], [Publisher]

[4] Mohapatra S.S., Wilson Z.E., Roy S., Ley S.V., Utilization of flow chemistry in catalysis: New avenues for the selective synthesis of Bis (indolyl) methanes, *Tetrahedron*, 2017, **73**:1812 [Crossref], [Google Scholar], [Publisher]

[5] Lee S.O., Choi J., Kook S., Lee S.Y., Lewis acid-catalyzed double addition of indoles to ketones:synthesis of bis (indolyl) methanes with all-carbon quaternary centers, *Organic & Biomolecular Chemistry*, 2020, **18**:9060 [Crossref], [Google Scholar], [Publisher]

[6] Athavale R., Gardi S., Choudhary F., Patil D., Chandan N., More P., Novel acidic ionic liquid [BEMIM][HSO_4]:A highly efficient and recyclable catalyst for the synthesis of *bis*-indolyl methane derivatives, *Applied Catalysis A:General*, 2024, **669**:119505 [Crossref], [Google Scholar], [Publisher]

[7] Galathri E.M., Kuczmera T.J., Nachtsheim B.J., Kokotos C.G., Organocatalytic Friedel–Crafts arylation of aldehydes with indoles utilizing N-heterocyclic iod (az) olium salts as halogen-bonding catalysts, *Green Chemistry*, 2024, **26**:825 [Crossref], [Google Scholar], [Publisher]

[8] Wai Chia P., Soon Lim B., Chen Tan Kh., Siong Julius Yong F., Kan S.Y, Water extract of onion peel for the synthesis of bisindolylmethanes, *Journal of King Saud University–Science*, 2019, **31**:642. [Crossref], [Google Scholar], [Publisher]

[9] Ali R., Ahamad M.Z., Singh S., Haq W., Regioselective synthesis of symmetrical and unsymmetrical bis (heteroaryl) methane (BHM)-containing amino acids, *European Journal of Organic Chemistry*, 2019, **2019**:1820 [Crossref], [Google Scholar], [Publisher]

[10] Kumbhar V., Raskar R., Chafle R., Nikam V., Kumbhar A., Pawar R., Chaskar M., Gugale G. Khairnar B., ProHSO_4:An efficient catalyst for solvent-free synthesis of bis (indolyl) methanes and their in silico screening for potential biological activity, *Results in Chemistry*, 2023, **6**:101023 [Crossref], [Google Scholar], [Publisher]

[11] Nguyen N.K., Ha M.T., Bui H.Y., Trinh Q.T., Tran B.N., Hung T.Q., Dang T.T., Vu X.H.,

Magnetically recyclable $CuFe_2O_4$ catalyst for efficient synthesis of bis (indolyl) methanes using indoles and alcohols under mild condition, *Catalysis Communications*, 2021, **149**:106240 [Crossref], [Google Scholar], [Publisher]

[12] Ghodrati K., Hosseini S.H., Mosaedi R., Karami C., Maleki F., Farrokhi A., Hamidi Z., Convenient, efficient, and green method for synthesis of bis (indolyl) methanes with nano SIO 2 under ultrasonic irradiation, *International Nano Letters*, 2013, **3**:1 [Crossref], [Google Scholar], [Publisher]

[13] Selvakumar K., Shanmugaprabha T., Annapoorani R., Sami P., One-pot three-component synthesis of bis (indolyl) methanes under solvent-free condition using heteropoly-11-tungsto-1-vanadophosphoric acid supported on natural clay as catalyst, *Synthetic Communications*, 2017, **47**:913 [Crossref], [Google Scholar], [Publisher]

[14] Kasar S.B., Thopate S.R., Synthesis of bis (indolyl) methanes using naturally occurring, biodegradable itaconic acid as a green and reusable catalyst, *Current Organic Synthesis*, 2018, **15**:110 [Crossref], [Google Scholar], [Publisher]

[15] Mhaldar S.N., Mandrekar K.S., Gawde M.K., Shet R.V., Tilve S.G., Solventless mechanosynthesis of *bis* (indolyl) methanes, *Synthetic Communications*, 2019, **49**:94 [Crossref], [Google Scholar], [Publisher]

[16] Khatab T.K., Abdelghany A.M., Soliman H.A., V_2O_5/SiO_2 as a heterogeneous catalyst in the synthesis of *bis* (indolyl) methanes under solvent free condition, *Silicon*, 2018, **10**, 703 [Crossref], [Google Scholar], [Publisher]

[17] Hasaninejad A., Zare A., Sharghi H., Khalifeh R., Zare A.R.M., PCl5 as a mild and efficient catalyst for the synthesis of bis (indolyl) methanes and di-*bis* (indolyl) methanes, *Bulletin of the Chemical Society of Ethiopia*, 2008, **22** [Crossref], [Google Scholar], [Publisher]

[18] Mallik A.K., Pal R., Guha C., Mallik H., A convenient, eco-friendly, and efficient method for synthesis of bis (3-indolyl) methanes "on-water",*Green Chemistry Letters and Reviews*, 2012, **5**:321 [Crossref], [Google Scholar], [Publisher]

[19] Dhumaskar K.L., Tilve S.G., Synthesis of bis (indolyl) methanes under catalyst-free and solvent-free conditions, *Green Chemistry Letters and Reviews*, 2012, **5**:353 [Crossref], [Google Scholar], [Publisher]

[20] Kidwai M., Chauhan R., Bhatnagar D., Nafion-H® catalyzed efficient condensation of indoles with aromatic aldehydes in PEG-water solvent system:A green approach, *Arabian Journal of Chemistry*, 2016, **9**, 2004 [Crossref], [Google Scholar], [Publisher]