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Efficient Synthesis of 3,3'-(Phenylmethylene)Bis-(2-phenyl-1H-Indoles) by Salicylic Acid as a Catalyst

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Abstract

It is very important today to conduct chemical reactions using the concept of green chemistry [1]. The paper develops an efficient and environmentally safe method for the synthesis of 3,3 '-(phenylmethylene)bis(2-phenyl-1H-indole) based on the condensation of 2-phenylenindole and benzaldehyde. In order to optimize the reaction conditions, the synthesis is carried out under different conditions. In particular, the reaction was carried out without solvent, in a water area, in a mixture of ethyl alcohol and water with different volume ratios, using a catalyst. It was found that in almost all cases the reaction went with high yield (> 85%). The duration of the reaction is remarkable. The best result was achieved, when we used water as a solvent: a mixture of ethanol in a ratio of 1: 1, and as a catalyst - salicylic acid (optimal amount of catalyst 15 mol%).

keywords: 2-phenylenindole , Bis(indolyl)methanes, Salicylic acids, Green synthesis

Introductions. Naturally occurring or synthetic BIMs and its privileged structures are particularly important in pharmaceutical chemistry as they exhibit various pharmacological activities and are important metabolites. BIMs display a wide range of biological activities such as antimicrobial and antifungal, antibacterial, analgesic and anti-inflammatory activities [1-9]. Besides antitumor and anticancer activities, BIMs have also been reported to be able to promote beneficial estrogen metabolism, promote useful estrogen, and induce apoptosis in human cancer cells. different methods have been reported for the preparation of BIMs are known. These methods have their merits in some way as claimed, but, on the other way, they suffer from certain drawbacks; e.g. harsh reaction

conditions, expensive use of catalyst, sensitivity to moisture and air, incompatibility of functional groups. Hence, there is still a need to search for better catalysts in terms of toxicity, handling, availability, economic viability, and operational simplicity. In view of the recent trend in catalytic process which comes under the purview of green chemistry, investigations for new and less hazardous catalysts have become a priority in synthetic organic chemistry.

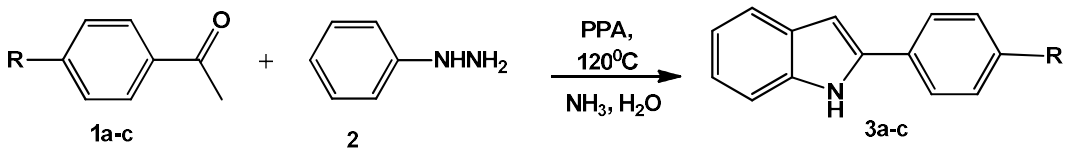
Aim. Herein, we report on the efficient green synthesis of BIMs (3) (Scheme 2) from 2-phenylindole (1) and Benzaldehydes (2) catalyzed by salicylic acid (SA).

Results and discussion

The aim of our research is to study the condensation reactions of 2-phenylindoles and various aromatic aldehydes in the presence of environmentally friendly solvents and catalysts. For the model reaction, we chose unsubstituted 2-phenyl-indole (3) and benzaldehyde (5) as starting reagents.

2-phenylindole was formed by Fischer indole synthesis from a condensation reaction of a phenylhydrazine and acetophenone in the presence of an acid catalyst in one step. (Scheme 1).

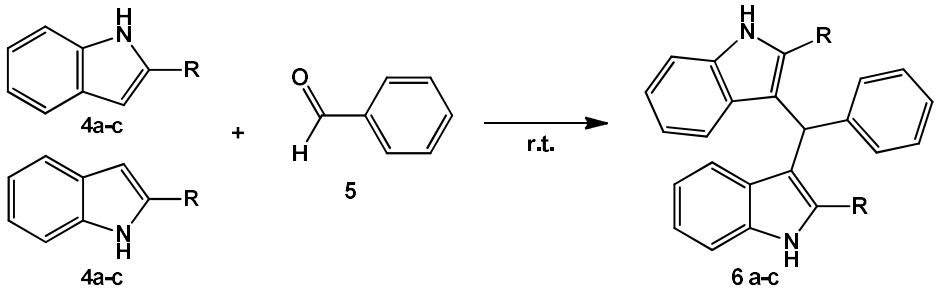
Scheme 1. Synthesis of 2-phenylindole



Ra-c = C_6H_5; C_6H_5-Br; C_6H_5-OCH_3

We carried out the synthesis of the target bis-indolyl-phenyl-methane both without solvent, by rubbing the reactants, and in environmentally safe solvents, water and ethanol, at room temperature. Product isolation from the resulting emulsion-like material gave a pure compound, characterization of which from analytical and spectral data showed it to be 3,3'-(phenylmethylene)bis(2-phenyl-1H-indole). (**Scheme 2).**

Scheme 2. Synthesis of 3,3 '- (Phenylmethylene)Bis-(2-Phenyl-1H-Indoles)



R_{a-f}= C_6H_5; p-Br-C_6H_4; p-OCH_3-C_6H_4;

First, reaction was carried out using H_2O and a mixture of H_2O-EtOH (v:v, 1:1) solvents in the absence of catalyst at room temperature (r.t.), which leads to the formation of product (6) in trace yields (Table 1, entries 1 and 2). The reaction in the presence of SA in H_2O gave 6 in 70% yield for 72 h (Table 1, entry 3). The best result was achieved in the case of a mixture of ethanol:water, 1:1, with the catalytic action of salicylic acid (15 mol %). (**Table 1**).

Table 1

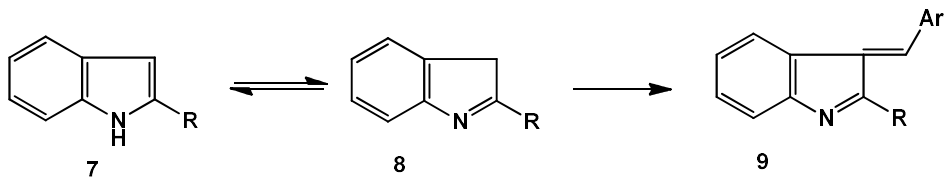
Optimization of the reaction conditions for the synthesis of 6a

Entry	Catalyst[a] (mol%)	Solvent	Time[b] (h)	Yield[c] (%)
1	-	EtOH-H_2O (1:1, v-v)	24	trace
2	-	H_2O	24	trace
3*	15	H_2O	72	70
4*	15	EtOH	48	62
5*	15	EtOH-H_2O (1:1, v-v)	24	90
6	-	-	120	95

[a] *salicylic acid (SA);* [b] *Reaction progress was monitored with TLC analysis;* [c]*Isolated yield of product.*

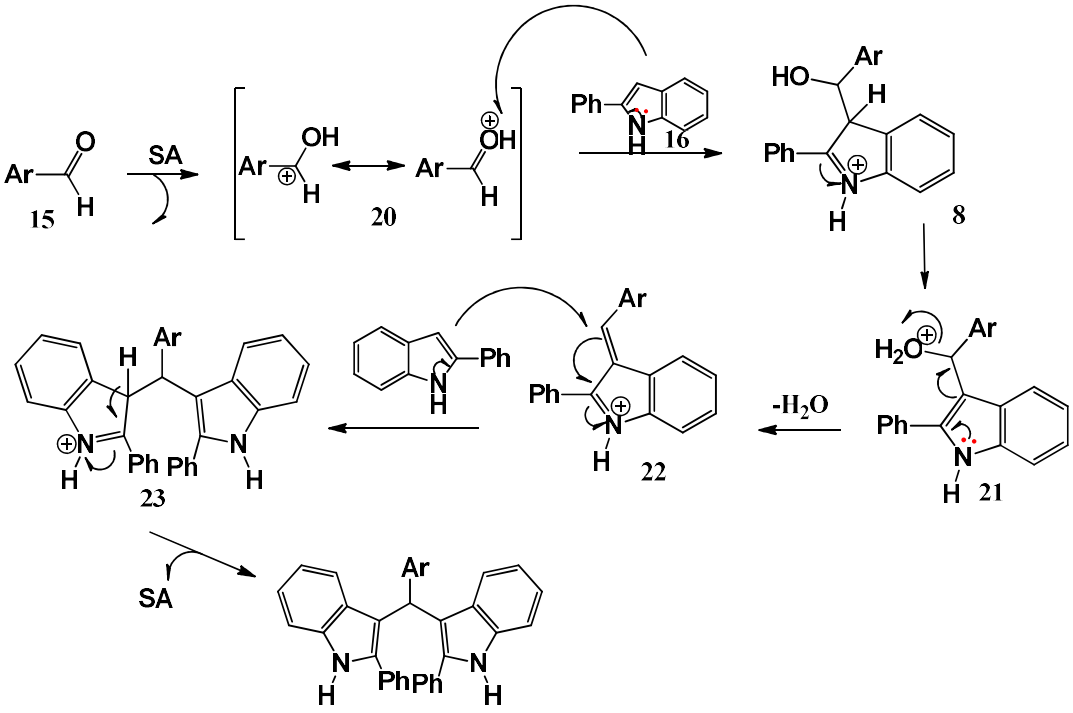
It is noteworthy that when the reactants were mixed, the reaction mixture initially acquired a reddish color, which gradually turned white. It is known from literary sources that N-unsubstituted indoles, when interacting with aldehydes, in a ratio of 1:1, in the presence of hydrochloric acid, give dyes, the so-called benzylidineindoles (9). This is due to the fact that the aldehyde does not react with indole, but with its tautomeric, indolenine form (8). (Scheme 3).

Scheme 3



In our opinion, a similar phenomenon occurred in our case, initially a red monomer product was obtained, which, when interacting with the second indole molecule, was transformed into the target product. Our opinion is also confirmed by the probable mechanism of the reaction (Scheme 4):

Scheme 4



SA - salicylic acid

The reaction proceeded with good yield when Compound 4 and 5 were mixed and grounded in a mortar with a pestle at room temperature for 15 min without any solvent. The procedure offers some advantages, but required long reaction time.

Methods Materials.

Instruments and Characterization. Melting point are determined using an A&E Lab DMP-800 melting point apparatus. The progress of reactions was monitored by TLC using silica gel plates under UV light (TLC Silica gel 60 F_{254} Merk). 1H and 13C nuclear magnetic resonance (NMR) spectra are recorded in *d*6-DMSO solution on a BRUKER AVANCE (400 MHz) instrument using tetramethylsilane as an internal standard, and chemical shift values (δ) are reported in parts per million.

All reagents are commercially available and purified according to the standard methods prior to use.

General Procedure for Synthesis of bis(3-indolyl)methanes. 2-phenylIndole **1** (2 mmol), Benzaldehyde **2** (1 mmol), and SA (15 mol%) were placed in a flask and H_2O-EtOH (1:1mL) was added. The reaction mixture was stirred at room temperature. After completion of the reaction (using TLC analysis), the solid was formed. The resulting solid product was filtered off, washed with small amounts of distilled water, dried, and recrystallized from hot ethanol.

3,3 '- (phenylmethylene)bis(2-phenyl-1H-indole) (6a). White crystals, Yield 95%, **IR** (KBr, cm^{-1}): 3419, 1599, 1488, 1447, 1341, 1307, 1235, 1018, 830, 741, 698, 667; **^{1}H NMR** (400 MHz, DMSO-d6): δ = 11.04 (s, 2H), 7.37 (d, *J* = 8.1 Hz, 2 H), 7.34 – 7.21 (m, 7H) , 7.20 (dd, *J* = 4.2, 2.3 Hz, 9H), 7.04 – 6.96 (m, 2H), 6.89 (d, *J* = 8.1 Hz, 2H), 6.71 – 6.63 (m, 2H), 6.06 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d6): δ =145.98, 136.88, 135.95, 133.49, 129.29, 128.83, 128.63, 128.52, 127.57, 126.35, 121.26, 121.22, 118.88, 114.81, 111.70. mp - 264-265°C.

3,3'-(phenylmethylene)bis(2-(4-bromophenyl)-1H-indole) (6b): white solid, m.p. 239-240 °C. IR (KBr, cm^{-1}): 3377, 1448, 1306, 1235, 1067, 1007,981, 965, 835, 815, 745, 699. ^{1}H NMR (400 MHz, DMSO): δ = 11.36 (s, 2H), 7.41 (d, *J* = 8.1 Hz, 4H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.28 (q, *J* = 9.0, 8.1 Hz, 3H), 7.19 (d, *J* = 7.2 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 4H), 7.02 (t, *J* = 7.6 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 6.69 (t, *J* = 7.6 Hz, 2H), 5.95 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ =145.08, 136.75, 134.67, 132.33, 131.64, 130.47, 129.15, 128.80, 129.29, 126.72, 121.69, 121.16, 121.23, 199.15, 115.04, 111.89.

3,3'-(phenylmethylene)bis(2-(4-methoxyphenyl)-1H-indole) (6c): white solid, m.p. 257-259 °C. IR (KBr, cm^{-1}): 3396, 1504, 1491, 1458, 1430, 1248, 1180, 1037, 840, 833, 749, 707. ^{1}H NMR (400 MHz, DMSO): δ = 11.23 (s, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.25 (dd, *J* = 11.7, 7.7 Hz, 7H), 7.13 (d, *J* = 7.4 Hz, 2H), 6.98 (t, *J* = 7.5 Hz, 2H), 6.89 (d, *J* = 8.2 Hz, 2H), 6.80 (d, *J* = 8.3 Hz, 4H), 6.66 (t, *J* = 7.6 Hz, 2H), 5.88 (s, 1H), 3.72 (s, 6H). ^{13}C NMR (100 MHz, DMSO): δ =143.48; 135.99; 135.66; 132.87; 130.64; 128.60; 128.42; 128.37; 128.24; 127.60; 121.85; 121.63; 119.71; 115.02; 110.68

Conclusions. In conclusion, we have developed an efficient electrophilic substitution reaction of 2-phenylindole with Benzaldehyde. The procedure offers several advantages including improved yield of products with no by-product's formation, simple experimental procedure with an economic and environmentally friendly solvent-free conditions and use of inexpensive catalyst;

Acknowledgments

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აბსტრაქტი

დღეისათვის ძალზედ აქტუალურია ქიმიური რეაქციების წარმართვა მწვანე ქიმიის კონცეფციის გამოყენებით. ნაშრომში 2-ფენილიინდოლისა და ბენზალდეჰიდის კონდენსაციის საფუძველზე შემუშავებულია 3,3'-(ფენილმეთილენ)-ბის-2-ფენილ-1H-ინდოლის სინთეზის ეფექტური და ეკოლოგიურად უსაფრთხო მეთოდი. რეაქციის პირობების ოპტიმიზაციის მიზნით, სინთეზი ჩატარებულია სხვადასხვა პირობებში. კერძოდ, რეაქცია ჩატარებული იქნა გამხსნელის გარეშე, წყლის არეში, სხვადასხვა მოცულობითი თანაფარდობის მქონე ეთილის სპირტისა და წყლის ნარევში, კატალიზატორის გამოყენებით. აღმოჩნდა, რომ თითქმის ყველა შემთხვევაში რეაქცია წავიდა მაღალი გამოსავლიანობით (> 85%). აღსანიშნავია რეაქციის ხანგრძლივობა. საუკეთესო შედეგი მიღწეულ იქნა იმ შემთხვევაში, როდესაც გამხსნელად გამოვიყენეთ წყალი : ეთანოლის ნარევი, თანაფარდობით 1:1, ხოლო კატალიზატორად - სალიცილის მჟავა (კატალიზატორის ოპტიმალური რაოდენობა 15 მოლი %).