Indian Journal of Chemistry
Vol. 61, October 2022, pp. 1120-1123
DOI: 10.56042/ijc.v61i10.67208

An efficient sodium chloride-catalyzed synthesis of bis(indolyl) methanes in green solvent and their antibacterial evaluation

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Received 14 April 2021; accepted (revised) 22 August 2022

A series of bis(indolyl)methanes derivatives have been synthesized using an efficient sodium chloride-catalyst in aqueous medium. Herein, substituted aldehydes have been successfully condensed with indole in an aqueous medium. Sodium chloride serves as an efficient and green catalyst as it is freely available and environmentally benign. Water used as green solvent also has no negative impact on the environment. The experiment follows a simple reaction procedure and completion of the reaction is achieved within 3-4 hours. The synthesized compounds have also been evaluated for their *in vitro* antibacterial property using 4 strains of bacteria, namely *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella pneumonia* where Streptomycin is used as the reference standard.

Keywords: Bis(indolyl)methanes, Aldehydes, NaCl, Aqueous medium, Antibacterial

Indole is found to be present in many natural products, agrochemicals and pharmaceuticals. In pharmaceutical field, indole and their derivatives have been identified as a significant compound because of possessing many promising biological activities[1,2]. Among the various derivatives of indole, bis (indolyl) methanes (BIM's) possess a wide range of medicinal application such as: to induce apoptosis in human cancer cell and normalize abnormal cell growth associated with cervical dysplasia[3], to promote beneficial estrogen metabolism in both women and men, to prevent breast cancer[4] and increase the natural metabolism of body hormone[5]. Bis(indolyl) methanes were found to possess antimicrobial activities against *Rhodopseduomonas fp.* and *E. coli* [HD701][6]. It was found that indole derivatives, 3,3-diindolylmethane (A) and 2-(indol-3-yl-methyl)-3,3-diindolylmethane (B) (Fig. 1) possess various pharmacological activities and they are also applied for the treatment of fibromyalgia, chronic fatigue and irritable bowel syndrome[7]. Due to possessing many biological activities, numerous researches have been carried out for the synthesis of BIM's and its derivatives and several procedures for the synthesis of these compounds have been reported in the literature. Various catalyst has been used which are reported in the literature for the synthesis of bis indole methane that includes $InCl_3$[8], In $(OTf)_3$[9], InF_3[10], $Dy(OTf)_3$[11], $Ln(OTf)_3$[12], $LiClO_4$[13], Zeokarb-225[14], molecular iodine[15,16], montmorillonite K10[17,18], $NbCl_5$[19], $FeCl_3$[20], $TiCl_4$[21], sodium bisulphate[22], tetra butyl ammonium tribromide[23], PEG-supported sulphonic acid[24], glycerine-$CeCl_3.7H_2O$[25]. However, most of the reactions face some serious drawbacks such as requirement for a large quantity of catalyst, longer reaction time, poorer yield and deposition of large amount of toxic waste during work-up. After going through several scientific research findings, uses of sodium chloride as a catalyst has been so far unexplored. So, in this present work we have synthesized some BIM's in aqueous medium which is eco-friendly by using the easily available, biodegradable and non-toxic sodium chloride as catalyst. Substituted Bis(indolyl) methanes derivatives were prepared according to the known procedures by the condensation of indole and aldehydes.

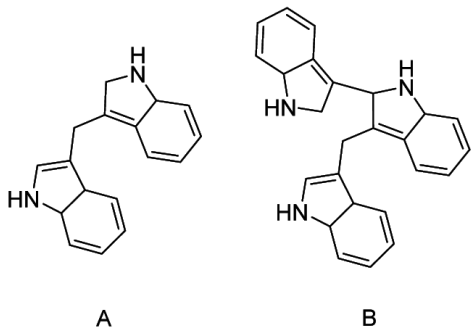


Fig. 1 — Pharmacologically active BIMs

Experimental Section

All reagents were purchased from Merck and used without further purification. Melting points were determined in open capillary tubes with JSGW apparatus and were uncorrected. The products were characterized by IR spectra, ^{1}H and ^{13}C NMR spectra, IR spectra were recorded on FT-IR Perkin Elmer, ^{1}H NMR and ^{13}C NMR were recorded on a FT-NMR Bruker Avance-II spectrometer using $CDCl_3$ and MeOD as a solvent. Chemical shifts are reported in ppm downfield using TMS as internal standard. All reactions were monitored by TLC using Silica Gel GF 254 and developed in an iodine chamber. Column chromatography separations were carried out using Silica Gel 60-120 mesh.

General procedure for the synthesis of bis (indolyl)methanes

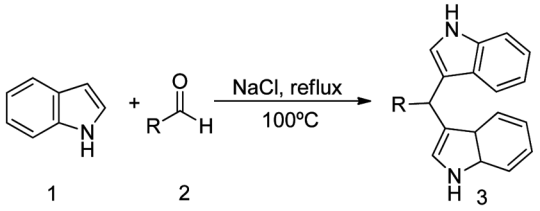
A mixture of indole (6.83mmol) and benzaldehyde (4.27mmol) were taken in a round bottom flask and 10 mL of water and (0.2mmol) of NaCl were added. The reaction mixture was refluxed at 100°C for 3-4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was extracted by ethyl acetate and the solvent was removed under reduced pressure. The crude product was then purified by column chromatography using ethyl acetate: hexane, to afford the pure product. The synthesized compound was then confirmed by spectral analysis data. The physical data (mp, IR, NMR, Mass spectra) of these compounds were found to be identical with those reported in the literature.

General procedure for the antibacterial test

For the *in vitro* antibacterial study of the synthesized compounds Well diffusion method was used where the activity of the compounds were determined by measuring the diameter of the inhibited zone (in mm)[26]. The microorganisms used in this study were two gram-positive bacteria *viz*. *Bacillus subtilis* and *Staphylococcus aureus* and two gram-negative bacteria *viz*., *Escherichia coli* and *Klebsiella pneumonia.* A concentration of 2 mg/mL of DMSO was prepared for all the test compounds where DMSO was used as a negative compound and Streptomycin was used as a negative control/the reference standard.

Results and Discussion

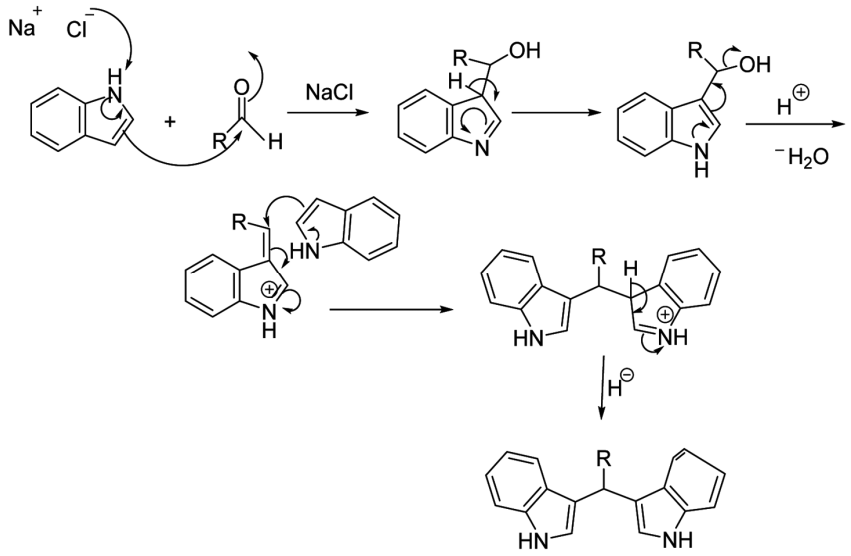
In this work, we have presented a simple and clean procedure for the synthesis of Bis (indolyl) methanes in aqueous medium employing inexpensive, eco-friendly, easily available, non-toxic sodium chloride as an efficient catalyst. The reactions were carried out at reflux condition and were completed within a short period of time. During the course period of reaction, the reactants were observed immiscible with water but with the progress of the reaction, the miscible of the reactants were observed and completions of the reactions were confirmed by TLC (Scheme 1, Table 1). In the presence of catalyst sodium chloride, the initial product of the reaction is azafulvenium salt, and then undergo further reaction with the second molecule of indole to produce bis (indolyl) methanes[27-29]. As the reaction proceed with an excess amount of indole (2 equiv), at the end of the reaction small amount of indole was left out which was further recovered by column chromatography. In order to avoid this, only 1.6 equiv. of indole was used instead



Scheme 1 — Synthesis of bis(indolyl)methanes

Table 1 — Synthesis of bis(indolyl)methanes from the condensation of indole and substituted aldehydes in an aqueous medium using NaCl as a catalyst

Compound	R-CHO	Time (h)	Yield (%)	m.p. (°C)
3a	C_6H_5	2	86	145-150
3b	4Cl-C_6H_4	1.5	75	74-76
3c	2Cl-C_6H_4	1.5	78	130-140
3d	3NO_2-C_6H_4	2	75	258-260
3e	Cinnamaldehyde	3	65	110-115
3f	2OH-C_6H_4	4	55	118-120
3g	3OH-C_6H_4	4	76	90-100
3h	3$OCH_3C_6H_4$-	2	69	186-188
3i	2-Furan	2	75	324-326
3j	4-N$(CH_3)_2C_6H_4$	3	88	224-226



Scheme 2 — Plausible mechanism for the formation of BIM

Table 2 — Anti-bacterial activity of the compounds (Diameter of zone of inhibition in mm)

Compound (2 mg/mL DMSO)	Zone of Inhibition (mm)			
	BS	EC	KP	SA
3a	11	10	12	13
3b	10	NI	>10	13
3c	11	10	12	13
3d	11	13	12	14
3e	10	NI	11	10
3f	18	17	19	16
3g	19	17	19	19
3h	>10	NI	10	11
3i	12	14	14	14
3j	11	11	11	>10
Streptomycin	23	22	22	22

NB.: NI- No Inhibition

B.s.: *Bacillus subtilis*, E.c.: *Escherichia coli*, K.p.: *Klebsiella pneumonia*, S.a.: *Staphylococcus aureus*.

of 2 equiv. It has been observed that the electronic properties of the aromatic ring affect the rate of the reaction; electron- withdrawing group (NO_2, Cl) in aldehydes enhances the electrophilic substitution reaction with a lesser reaction time than electron donating groups.

The mechanism of the BIM formation has been reported where azafulven is produced as an intermediate which undergoes addition with a second indole molecule to produce BIMs[30] (Scheme 2).

Representative characterization data

3-(4-Chlorophenyl)(1*H*-indol-3-yl)methyl-1*H*-indole, 3b: m.p.74-76°C. IR (KBr): 3412 (NH), 3190 (Ar-CH), 2977 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.86 (s, 1H, CH), 6.6 (s, 2H, 2×ArH), 6.9-7.3 (m, 12H, ArH), 7.9 (s, 2H, 2×NH); ^{13}C NMR ($CDCl_3$): δ 60.57, 111.25, 119.29, 119.94, 122.19, 123.74, 126.99, 128.49, 130.20, 131.90, 136.81, 142.69, 171.3; MS: *m/z* 355$[M]^+$, 356$[M+1]^+$.

All the synthesized compounds were screened for their antibacterial activity and the results are as shown in Table 2. The test revealed that almost all the compounds showed good activity against all bacterial strains except for R2, R5 and R8 which showed no inhibition to *Escherichia coli*. Compounds R6 and R7 showed very promising results as they showed the best activity against all the bacterial strains.

Conclusion

The scope of application for the present method is justified by the reaction of Indole with various

aldehydes to give corresponding bis (indolyl) methanes where the structures were confirm by several spectral analysis. Herein we also developed using NaCl as efficient, eco-friendly and convenient catalyst for the synthesis of Bis (indolyl) methane. Besides being cost effective, this approach is easy work-up and eco-friendly protocol. Also almost all the synthesized compounds which were screened for their antibacterial property showed promising result especially compound R6 and R7 proving to be a good antibacterial potent.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

Acknowledgement

The authors gratefully acknowledge the Pondicherry University and Sophisticated Analytical Instrument Facility (SAIF), North-Eastern Hill University (NEHU), Shillong for the spectral analysis and UGC, New Delhi for Non-NET Fellowship.

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