

**CHITOSAN HYDROCHLORIDE: AN EFFICIENT, RECYCLABLE ACID
CATALYST FOR THE SYNTHESIS OF 3, 3'-DIINDOLYLMETHANES
FROM ALDEHYDES AND INDOLES IN WATER.**

Premchand B. Shelke

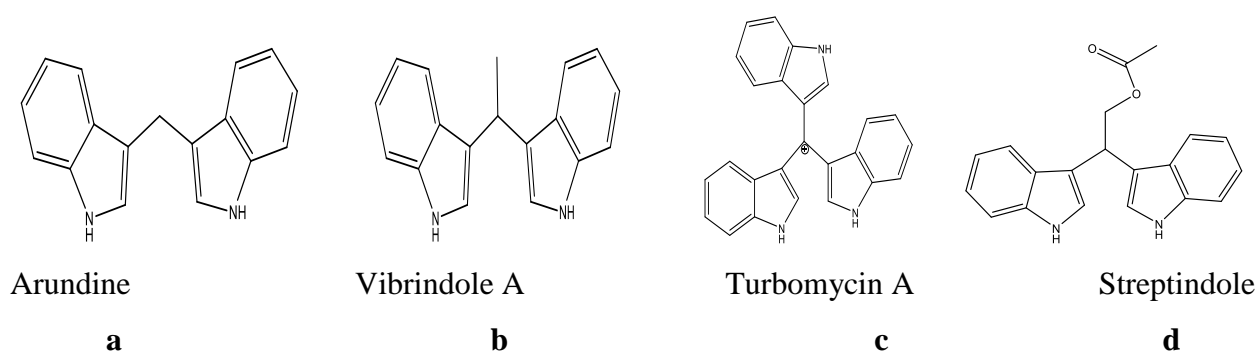
Department of Chemistry, Kirti M. Doongursee College, Mumbai-400028, India.

Abstract: Chitosan hydrochloride has been employed for the synthesis of diindolylmethanes (DIMs). It is a biodegradable, efficient and eco-friendly catalyst for the present work. Good catalytic performance, catalyst recyclability, ease of product isolation, good to excellent yields, shorter reaction time are some of the major advantages offered by the developed protocol.

Keywords: chitosan hydrochloride, diindolylmethanes, catalyst, recyclability.

1. Introduction:

Nitrogen based heterocycles widely occur in nature. Many of these formulate the moieties of naturally occurring or synthetic drug molecules. These heterocycles exhibit wide range of therapeutic properties. Specifically, indole derivatives i.e. diindolylmethanes have been reported to show numerous medicinal applications. Compounds **a** and **b** (Scheme 1) are diindolylmethane based naturally occurring drug molecules while structures **c** and **d** (Scheme 1) represent diindolylmethane based synthetic drug molecules (**Scheme 1**).



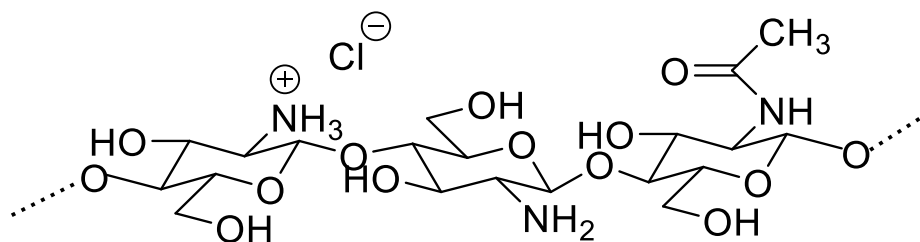
Scheme 1: Natural and synthetic diindolylmethanes.

The diindolylmethanes have gained tremendous importance owing to their wide spectrum of biological and medicinal properties. They exhibit analgesic, anti-inflammatory¹, antimicrobial, antifungal² and antibacterial³ properties. More importantly, they are known to increase the natural metabolism of human body hormones⁴ whereby they promote estrogen metabolism in men and women controlling breast cancer⁵ and normalize abnormal growths in cervix⁶ etc.

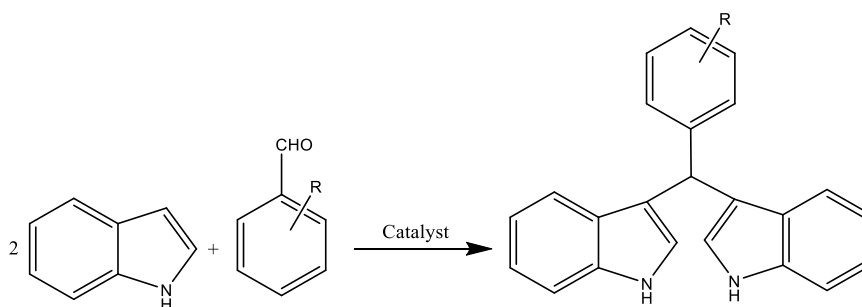
Various methods for the synthesis of diindolylmethanes have been reported in the literature. Hasaninejad et. al. have reported the synthesis of diindolylmethane using picric acid as catalyst at room temperature in aqueous media⁷. Shaikh et. al. have synthesized diindolylmethane by grinding a mixture of indole and benzaldehyde in a mortar with pestle in presence of $\text{SnCl}_2 \cdot \text{H}_2\text{O}$ catalyst⁸. Dabiri et. al. have reported the synthesis of diindolylmethanes from indole and carbonyl compounds by using ionic liquids $[\text{Hmim}]\text{Tfa}$ and $[\text{Hmim}]\text{HSO}_4$ as catalysts at room temperature⁹. Vaghei et. al., have disclosed the synthesis of diindolylmethanes from indole and different aldehydes and ketones by using catalysts like poly(*N,N'*-dichloro-*N*-ethyl-benzene-1,3-disulfonamide) [PCBS] and *N,N,N',N'*-tetrachlorobenzene-1,3-disulfonamide [TCBDA] under solvent and solvent-free conditions¹⁰ Sujatha et. al. synthesized diindolylmethane from indole and aldehyde by using NaHSO_4 in ethanol-water solvent¹¹.

A typical diindolylmethane synthesis involves acid catalyzed condensation of two moles of indole with one mole of carbonyl compound in the presence of Bronsted or Lewis acid. Numerous catalysts have been explored till date for the synthesis of diindolylmethanes employing various Bronsted acid and Lewis acid catalysts like $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ ¹², ZrCl_4 ¹³, InCl_3 ¹⁴. Besides, other catalysts employed are acetic acid¹⁵, CAN ¹⁶, CuBr_2 ¹⁷, oxalic acid¹⁸, ion exchange resin¹⁹, LiClO_4 ²⁰, H-Y Zeolite²¹, $\text{In}(\text{OTf})_3$ ²², $\text{Zn}(\text{HSO}_4)_2$ ²³, $\text{Cu}(\text{BF}_4)_2 \cdot \text{SiO}_2$ ²⁴, sulphamic acid²⁵, SBA-15/ SO_3H ²⁶, Ph_3CCl ²⁷, $\text{Bi}(\text{NO}_3)_3$ ²⁸, polyindole salt²⁹, glycerine and CeCl_3 ³⁰, $\text{Dy}(\text{OTf})_3$ ³¹, ZrOCl_2 ³², PFPAT³³, trichloro-1,3,5-triazine³⁴, HFIP³⁵, KHSO_4 ³⁶, molecular iodine³⁷. Most of the catalysts offer good to excellent yields. However, in the view of growing environmental concerns, the use of corrosive mineral acids, costly and toxic metal catalyst, longer reaction time, tedious work-up, formation of large amount of wastes and hazardous byproducts, non-recyclability in few cases and overall negative environmental impact limit their applications while producing the important diindolylmethane derivatives on a commercial scale.

Recently, chitosan hydrochloride, a biodegradable polymer obtained from chitin, has attracted much attention in the realm of heterogeneous catalysis. Chitosan is a natural biopolymer which consists of a linear polysaccharide made up of 2-amino-2-deoxy-D-glucopyranose units linked to each other via glycoside bonds. **Scheme 2** depicts the structure of chitosan hydrochloride. Few organic transformations such as Heck reaction³⁸, Ullman reaction³⁹, Suzuki cross-coupling⁴⁰, Michael addition⁴¹, Knoevenagel condensation⁴², etc. are successfully carried out by using chitosan hydrochloride. Thus, considering the drawbacks associated with conventional protocols and knowing the advantages of chitosan hydrochloride, herein we take this opportunity to demonstrate a facile and environmentally benign method for diindolylmethane synthesis.



Scheme 2: Structure of chitosan hydrochloride



Scheme 3: Synthetic protocol for diindolylmethanes

2. Experimental:

2.1 Materials and methods

All the required chemicals were purchased from commercial sources (Sigma-Aldrich & Merck) and were used without further purification. The purities of the derivatives were checked by thin-layer chromatography (TLC) (Silica gel H, British Drug Houses (BDH), ethyl acetate-hexane, 1:3). Melting points were determined using a calibrated thermometer by Guna Digital Melting Point apparatus.

2.2. Preparation of Chitosan hydrochloride:

Chitosan (1 g) was dissolved in 75 cm³ of 1% HCl with constant stirring and occasional heating. This solution was filtered to remove undissolved mass through cotton. The resultant filtrate was filtered under suction and allowed to dry.

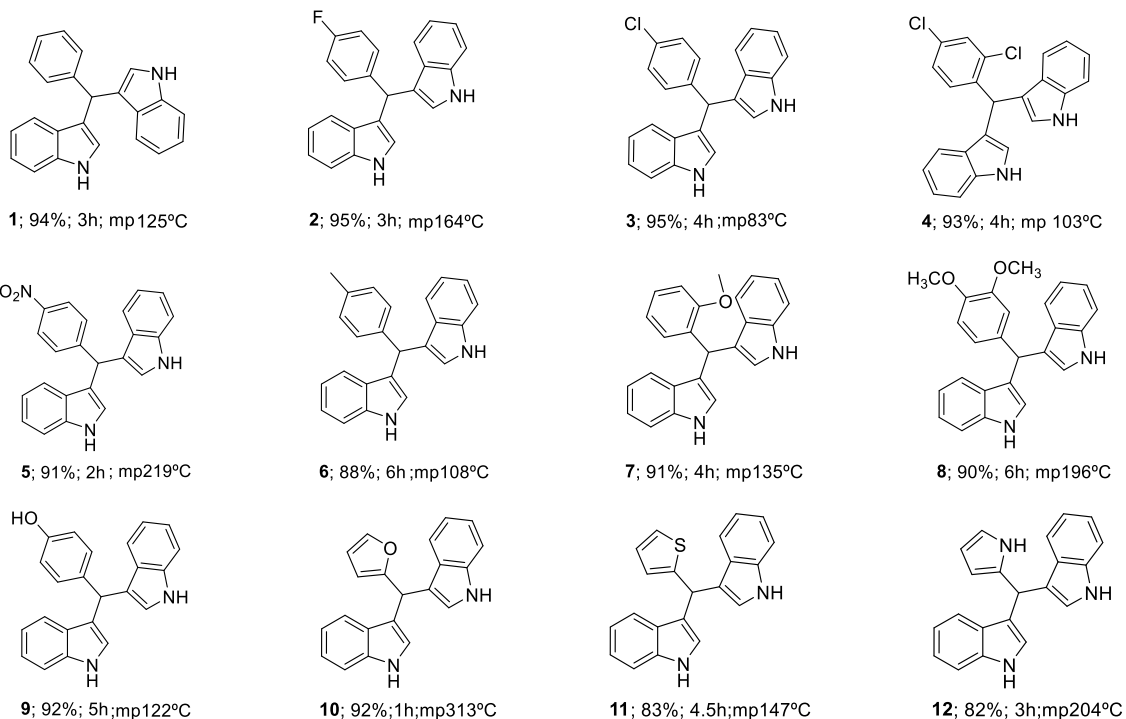
2.3. General procedure for the syntheses of diindolylmethanes:

Benzaldehyde (1mmole) was added to indole (2 mmole) and 0.100 g of Chitosan hydrochloride and 5 cm³ of water as a solvent and the mixture was stirred initially at room temperature. The reaction was monitored by TLC. The reaction was carried out then at different temperatures and the optimum temperature for the reaction was found to be 80°C. When the reaction completed, the reaction mixture was poured on ice-cold distilled water and stirred for 5-10 minutes. The crude product was filtered under suction, washed with water and recrystallized from hot ethanol

to obtain the pure diindolylmethane. The melting points of the derivatives were in agreement with those of the reported compounds. The yield of the product was 94%.

3. Results and Discussion:

3.1: Substrate scope



Scheme 4: Various diindolylmethane derivatives synthesized using chitosan hydrochloride.

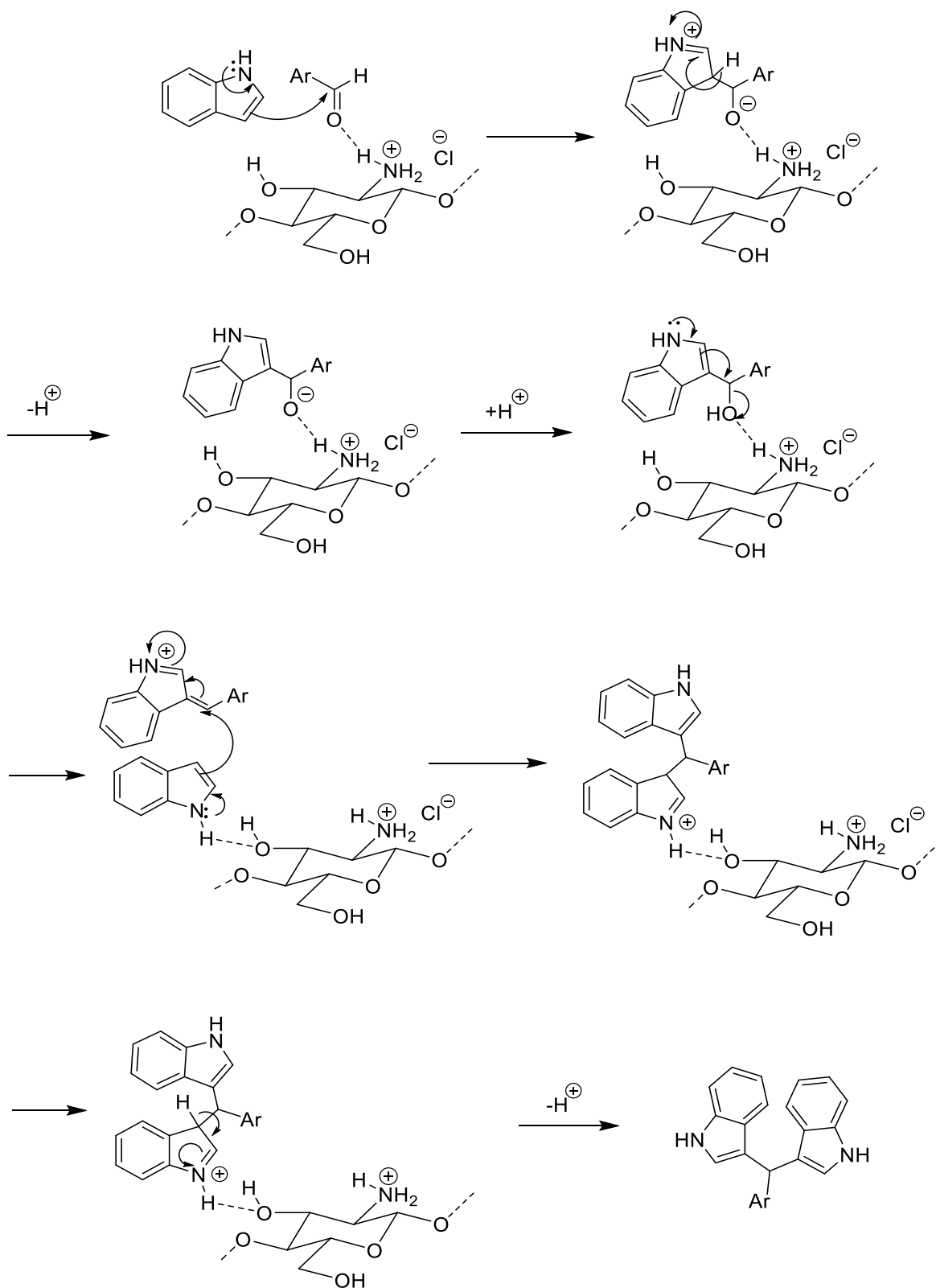
3.2. Recyclability study

Chitosan was recovered from the aqueous medium by addition of sufficient amount of ethyl alcohol and filtered. It was then dried and recycled five times without any significant loss in weight and activity (Figure 1).



Figure 1: Recyclability study of chitosan hydrochloride

3.3. Plausible reaction mechanism:



Scheme 5: Plausible mechanism for the synthesis of diindolylmethanes via the formation of azafulvenium ion.

4. Conclusion

In conclusion, we have developed environmental friendly and easily amenable to scale up synthetic protocol for diindolymethane synthesis in presence of biodegradable chitosan hydrochloride catalyst. The developed protocol is likely to substitute the existing diindolymethane syntheses methodologies.

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