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Cyanoacetic acid promoted an eco-expedient synthesis of bis(indolyl)methanes at ambient temperature condition

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ABSTRACT

Water mediated green reaction of indole with substituted aryl aldehydes in order to generate bis(indolyl)methanes using cyanoacetic acid as a catalyst has been established. High yields and a simple workup enable the convenient generation of the target compound at room temperature. Herein we have reported an efficiently inexpensive synthetic protocol to obtain these fascinating molecules which undoubtedly constitute a vital structural motif.

Keywords: Cyano Acetic acid, water, Bis(indolyl)methanes, Indole, aromatic aldehyde.

INTRODUCTION

Bis(indolyl)alkanes and their derivatives constitute an important group of biologically active synthetic molecules attributing to their diverse applicative approaches. Bis(indolyl)methanes and their derivatives are known to possess activities which affect central nervous system[1] and used as tranquilizers[2]. Also bis(indolyl)methanes are well known to exhibit anticholinergic activity[3]. Moreover 2, 4- Bis(indolyl) thiazole analogues exhibited cytotoxic activities against a wide range of human tumor cell lines at micro molar concentrations[4]. Similar antitumor properties reported by dragmacidin D[5]. Recently Lee and co-workers reported 1,1,3-tri(3-indolyl)cyclohexane which inhibit cancer cell of xenograft model[6].

Therefore, the clinical significance of this class of compounds stimulated interest of the researchers to delve out newer synthetic methodology every time with a considerable increase in approach towards greenness in synthesis. Synthesis of bis(indolyl)methanes which involves an electrophilic substitution reactions is carried out by using catalysts such as protic acid[7], Lewis acid[8], heteropoly acids[9] and heterogeneous catalysts[10]. Besides the conventional and microwave methods Xiao-Fei Zeng and coworker[11] have developed a simple, novel and an efficient synthetic protocol for synthesis of unsymmetrical BIMs using catalytic amount of cerric ammonium nitrate under ultrasonic irradiation at room temperature, With an increasing environmental concerns and regulatory constrains chemists are devoted to the area of green chemistry which has attained the status of a major scientific discipline[12]. Solvents are central feature, as they are generally used in large quantities; such a consideration has prompted synthetic organic chemists to explore the potential of water as a solvent for organic synthesis. Toward this end, considerable efforts have been devoted to develop and use nontraditional solvents for chemical synthesis[13]. Such unconventional medium include solvent-free conditions[14], supercritical carbon dioxide[15], ionic liquids, perfluorinated solvents[16], and last but most noteworthy of all is water. Dodecylbenzenesulfonic acid (DBSA)[17] and dodecylsulfonic acid (DSA)[18-19] also promote BIM formation from aldehydes and indoles in water. Yadav et.al, explored the utility of 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF4]) and 1-butyl-3-

methylimidazolium hexafluorophosphate ([bmim][PF6])[20]. However in spite of several innovations in the methodology, most of these synthetic protocols utilize a circuitous route, require longer reaction time, and are often associated with environment polluting aspects. Thus, on elaborating the idea of aqueous mediated system, there emerges a need for special catalyst system which homogenizes the water insoluble reactant to uniform phase by simultaneously catalyzing the reaction medium with a considerable abridgement of time required. In our ongoing endeavor to establish clean and eco-friendly synthetic methodologies[21], we wish to report herein cyanoacetic acid as an inexpensive, efficient and sustainable catalyst in presence of water at room temperature for the synthesis of Bis(indolyl)methanes. Cyano acetic acid has been sucessfully used as active methylene compound for preparing α,β-unsaturated nitriles and esters, for carbolactonization of alkenes to α-cyano γ-lactones, and for converting trans-1,2-bromohydrins to cis-1,2-diols[22].

MATERIALS AND METHODS

All chemicals and solvents were reagent grade and used as purchased without any further purification. Analytical thin-layer chromatography was performed on percolated silica gel 60-F 254 plates. The data found were in consistent with the proposed structure. IR spectra on KBr disks were recorded on a Schimazdu IR-470 FT-IR spectrophotometer. The routine nuclear magnetic resonance spectra were taken in CDCl3 using a Bruker Spectrospin Avance II-300 MHz spectrophotometer and Jeol-400MHz spectrophotometer with TMS as an internal standard. GCMS spectra analyses were done on Shimadzu QP 2010 GCMS. Melting points were determined in an open capillary tube and were found to be uncorrected.

General procedure:

To the solution of 15 mole% of cyanoacetic acid in water (20 ml) appropriate aldehyde (2 mmol) and indole (4 mmol) were added and the mixture was stirred at room temperature for the mentioned reaction time **(Table I)**. The product was isolated by simple filtration and further purified by column chromatography using solvent system [ethyl acetate / petroleum ether (1:9)] to get desired bis (indolyl) methanes in high yields.

Spectroscopic data of representative compound:

Bis(3-indolyl)-p-nitrophenylmethane (Table I Entry 6g):

1H NMR (CDCl3, 500 MHz): d (ppm) 5.92 (s, 1H, CH), 6.63 (s, 2H), 6.91 (t, J= 7.3 Hz, 2H, arom), 7.08 (t, J = 7.3 Hz, 2H, arom), 7.25 (d, J =7.9 Hz, 2H, arom), 7.32 (d, J= 8.1 Hz, 2H, arom), 7.44 (d, J =8.6 Hz, 2H, arom), 8.04 (d, J= 8.6 Hz, 2H, arom), 9.31 (s, br, 2H, NH). 13C NMR: d (ppm) 40.5, 111.8, 117.8, 119.4, 119.7, 122.1, 123.8, 124.4, 127.0, 129.9, 137.3, 146.7, and 152.8.

RESULTS AND DISCUSSION

To demonstrate the catalytic efficiency of cyanoacetic acid, initially we carried out a controlled reaction with an aromatic aldehyde (1mmol) and indole (2 mmol) without cyanoacetic acid and stirred for several hours. A sticky reaction mixture was obtained with the formation of bis (indolyl) methane in very low yield. In another experiment, aldehyde and indole were taken in 5 mL water to which 10mole% of cyanoacetic acid were added (Scheme I) and the reaction mixture was stirred at room temperature till the completion of reaction as monitored by TLC.

Scheme I

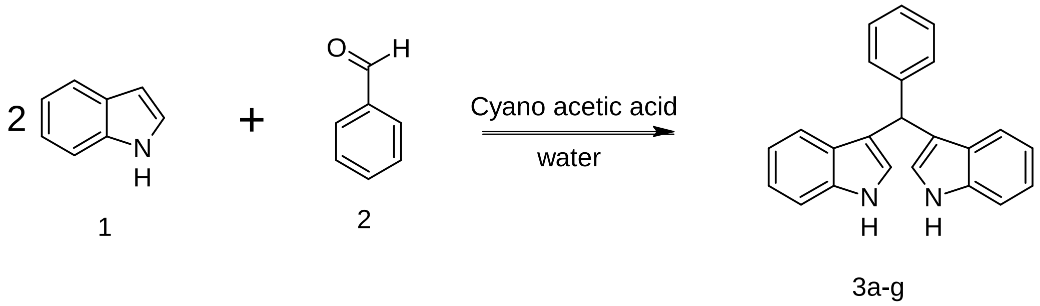
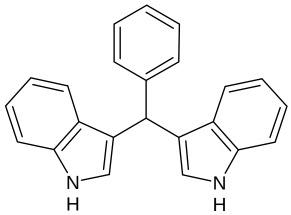
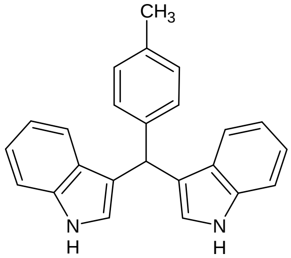
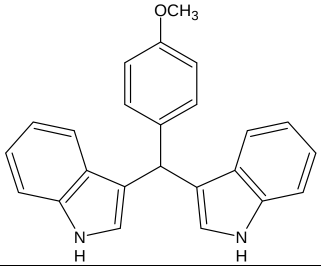
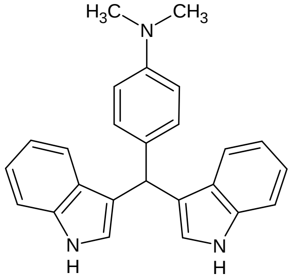
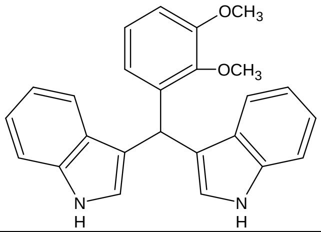
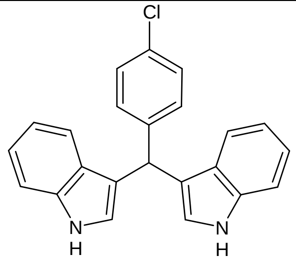
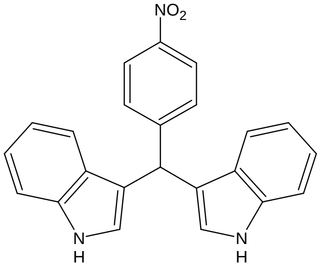


Table I: Synthesis of diversified Bis(indolyl)methane[a]

Entry	Compound	Time (min.)	Yield (%)[b]	M.P.	
				Observed	Literature
6a		55	89	126-128°C	125-127°C[23]
6b		70	90	92-95°C	94-96°C[23]
6c		75	87	185-188°C	187-189°C[23]
6d		90	83	171-173°C	170-172°C[23]
6e		65	91	218-220°C	220-222°C[23]
6f		50	91	79-81°C	77-81°C[23]

6g		65	91	219-220°C	218-220°C[24]

[a] Appropriate aldehyde: 2 mmol, Indole: 4 mmol, CAA: 0.3 mmol (15 mole%), Water: 20ml;
[b] Isolated yield.

The reaction proceeded cleanly and desired pink red colored bis(indolyl) methane was isolated in good yield. Inspired with the catalytic potential of CAA we examined the generality of this procedure on series of bis (indolyl)methanes **(Table I)**. Several aryl aldehydes with electron withdrawing and donating functional groups undergo efficient formation of the bis(indolyl)methanes in short reaction time. The product, bis(indolyl)methanes were obtained in good yields and were separated simply by filtration on vacuum pump. As reaction proceeds in water with good yields of the product, we were not interested to examine the feasibility of the reaction in other organic solvents.

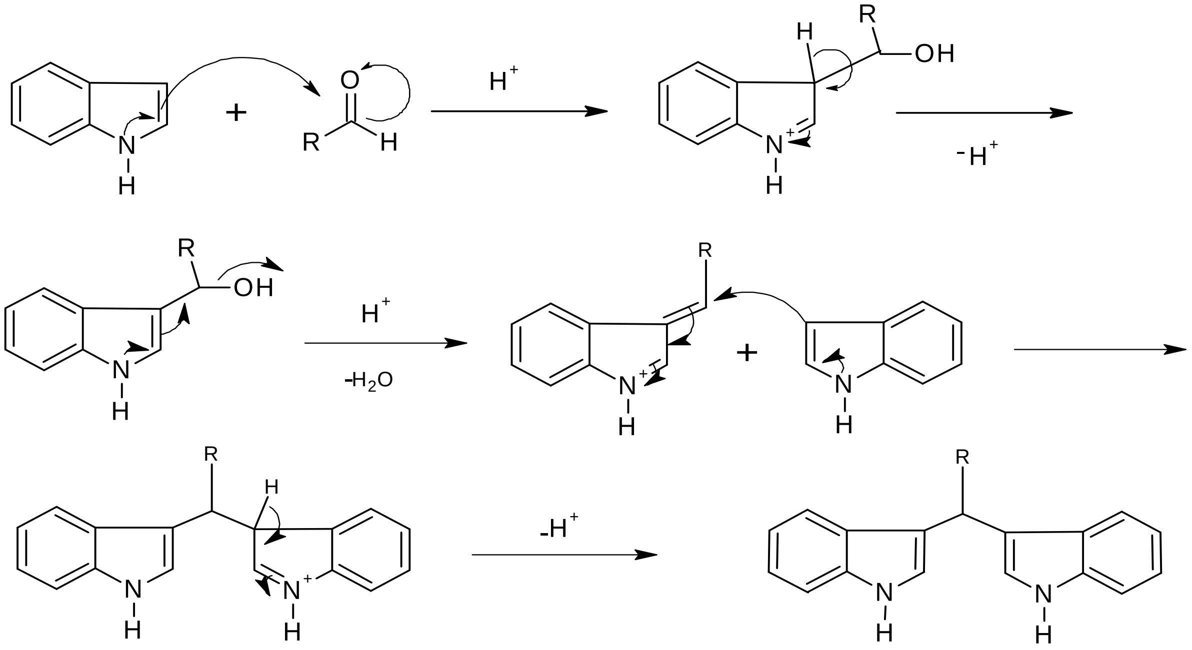
The Cyanoacetic acid catalyst was screened for its catalytic efficiency**(Table II)** comparing it with other resembling acids, fortifying to our expectations the CAA proved outstanding among the other appropriate catalysts for synthesis of the desired class of bis(indolyl)methanes.

Table II: Effect of catalysts on the synthesis of Bis(indolyl)methane derivative by reaction of 4-nitrobenzaldehyde and indole (entry 6g)

Sr. No.	**Catalyst**	**Solvent**	**Time (min)**	**Yield (%)**	**Reference**
1.	CSA	20% Ethanol-water	240	97%	24
2.	$ZrOCl_2.8H_2O$	20% Ethanol-water	300	95%	24
3.	Oxalic acid	20% Ethanol-water	360	81%	24
4.	p-TSA	20% Ethanol-water	300	80%	24
5.	CAA	Water	65	91%	This work

The results clearly indicate the generality and scope of this protocol showing the reactions of aromatic aldehydes with indole, which were smoothly converted to the corresponding bis(indolyl)methane in excellent yields. The reactions of aromatic aldehydes having electron withdrawing groups were somewhat faster than that of electron donating groups. The formation of the desirable BIMs was detected by their melting points and IR, ^{1}HNMR, ^{13}C NMR and mass spectroscopic methods.

Plausible Mechanism: Mechanism involving azafulvanium salts finally giving bis(indolyl)methane



CONCLUSION

Cyanoacetic acid was found to be a mild and efficient catalyst for the electrophilic substitution reaction of indole with various aromatic aldehydes affording corresponding bis(indolyl)methanes in excellent yields. The advantages of this protocol are mild reaction conditions with reduced amount of catalyst loading, high conversion, easy handling, efficient and clean synthesis, which makes the procedure attractive.

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