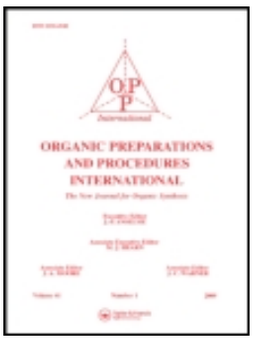

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Organic Preparations and Procedures International

The New Journal for Organic Synthesis

ISSN: 0030-4948 (Print) 1945-5453 (Online) Journal homepage: http://www.tandfonline.com/loi/uopp20

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To cite this article: Kandasamy Karthikeyan & Ganesabaskaran Sivaprasad (2015) Synthesis of some bis(Indolyl)methanes Catalyzed by Ascorbic Acid under Mild Conditions, Organic Preparations and Procedures International, 47:6, 449-453, DOI: 10.1080/00304948.2015.1088755

To link to this article: http://dx.doi.org/10.1080/00304948.2015.1088755

Published online: 30 Oct 2015.

Organic Preparations and Procedures International, 47:449–453, 2015

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Synthesis of some *bis*(Indolyl)methanes Catalyzed by Ascorbic Acid under Mild Conditions

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*bis(*Indolyl) derivatives exhibit tranquilizing,[1,2] anti-bacterial and anti-fungal activity[3] and indoles themselves are useful in the treatment of fibromyalgia, chronic fatigue and irritable bowel syndrome.[4–6] In addition *bis*-indoles are utilized as highly selective colorimetric and ratiometric fluorescent molecular chemosensors[7] and also in cancer chemotherapy.[8]

A wide variety of catalysts such as protic[9] and Lewis acids,[10–12] clays,[13] lithium perchlorate,[14] iodine,[15] Amberlyst resins,[16] trityl chloride,[17] cyanuric chloride,[18] as well as ionic liquids[19,20] have been utilized for the electrophilic substitution reaction of indoles with aromatic aldehydes to yield *bis*(indolyl)methanes. However, these reagents are not only expensive, their preparation requires long reaction times and results in low yields; furthermore, they are strongly acidic and may involve cumbersome experimental and isolation procedures. Ascorbic acid has been used as a C-nucleophile,[21] as an intermediate for the synthesis of chiral oxetanes and chiral polyols,[22] as a reductant[23,24] in the preparation of chiral platinum-*bis*-phosphinite complex catalysts,[25,26] and as a catalyst for the reductive desulfonylation of β-ketosulfones.[27] Therefore it was decided to explore its potential as a catalyst and we now report the successful condensation of indoles with several aromatic aldehydes.

The reaction, carried out at room temperature in ethanol, between indole and aromatic aldehydes in the presence of ascorbic acid, proceeded in better than 80% yield for aromatic aldehydes bearing both electron-donating and electron-with-drawing substituents (*Scheme 1*). However, under the same conditions aliphatic aldehydes such as acetaldehyde and propionaldehyde did not yield *bis*-indoles; cinnamaldehyde and crotonaldehyde only gave resinous products.

Ascorbic acid is economical and environmentally safe in contrast to Lewis acids which are expensive, moisture sensitive, and can interact and be deactivated by the NH of an indole. The use of this catalyst has the advantage of mild reaction conditions, and simple experimental and isolation procedures. In conclusion, we have developed a simple and efficient method for the preparation of *bis*(indolyl)-methanes using ascorbic acid whose potential as a catalyst remains largely unexplored.

Received March 7, 2105; in final form April 27, 2015.
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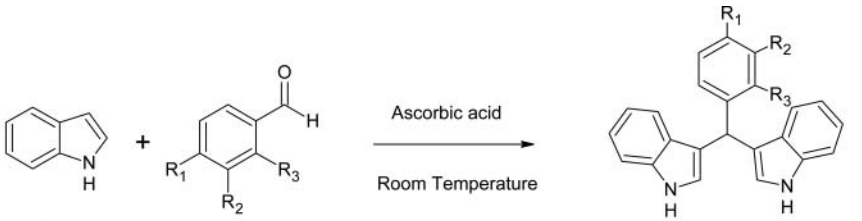


a) R = R_1, R_2, R_3 = H; b) R_1 = H, R_2 = NO_2, R_3 = H; c) R_1 = Cl, R_2 = H, R_3 = H; d) R_1 = H, R_2 = H, R_3 = Cl; e) R_1 = OCH_3, R_2 = H, R_3 = H; f) R_1 = OCH_3, R_2 = OCH_3, R_3 = H; g) R_1 = CH_3, R_2 = H, R_3 = H; h) R_1 = NO_2, R_2 = H, R_3 = H; i) R_1 = H, R_2 = H, R_3 = OH; j) R_1 = H, R_2 = OCH_3, R_3 = H.

Scheme 1 Synthesis of *bis*(Indolyl)methanes Catalyzed by Ascorbic Acid

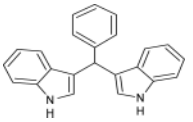
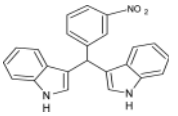
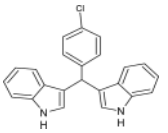
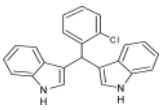
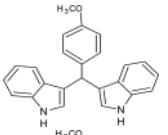
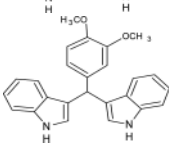
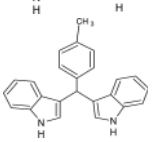
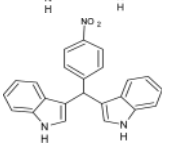
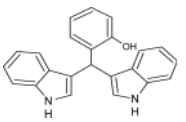
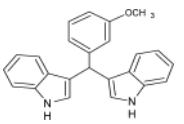
Experimental Section

Ascorbic acid, substituted benzaldehydes, indoles, silica gel (100–200 mesh), petroleum ether, ethyl acetate and ethanol were purchased from S. D. Fine Chemicals and used as received. Macherey-Nagel pre-coated plastic sheets coated with silica gel G/UV-254 of 0.2 mm thickness were used to perform analytical TLC. A mixture of petroleum ether-ethyl acetate (80:20) was used as the solvent system for elution. Mps were determined in capillary tubes on a Concord melting point apparatus and are uncorrected. A Perkin-Elmer Spectrum One FTIR/ATR spectrometer was used to obtain Fourier transform infrared spectra as KBr pellets. NMR spectra were acquired in $CDCl_3$ solutions (with TMS as an internal standard) on a Bucker Avance III instrument (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz). Mass spectra were measured using a Jeol GCMATE II GC-MS in EI mode. Combustion analyses were carried out using a Thermo Finnigan Flash EA 1112 series.

Typical Procedure

A mixture of indole (0.29 g, 2.5 mmol), benzaldehyde (0.13 g, 1.2mmol) and ascorbic acid (0.03 g, 0.17 mmol) in 10 mL of ethanol was stirred at room temperature in a round-bottomed flask for 30 min. The progress of the reaction was monitored by TLC [petroleum ether-ethyl acetate (80:20) Rf value = 0.169 for *bis*(indolyl)methane]. After that time, the reaction mixture was poured into crushed ice and the precipitated product was collected and purified using column chromatography on silica gel [elution with a mixture of ethyl acetate and petroleum ether (1:9)] to give 0.35g (89%) of **3a** as a pink solid. All the products are known compounds whose mps matched those reported in the literature (*see* Table 1).

Table 1
Synthesis of *bis*(Indolyl)methanes Catalyzed by Ascorbic Acid

Product	Compound	Yield (%)	mp. °C (*lit.*)	Ref.
	3a	89	125–127(125–126)	28
	3b	82	259–261(261–263)	32
	3c	80	75–76(76–77)	29
	3d	81	73–75(75–77)	33
	3e	90	188–190(187–189)	29
	3f	89	196–197(197–198)	30
	3g	87	94–96(95–97)	34
	3h	80	221–222(220–222)	28
	3i	84	343–345(342–344)	28
	3j	86	179–180(180)	31

All compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectra.

Acknowledgements

The authors thank the SAIF-IIT for instrumental analyses and gratefully acknowledge the Executive Editor, Professor J.-P. Anselme, for his patience, corrections and continuous suggestions in writing this manuscript.

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