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Applied Chemistry

Elixir Appl. Chem. 70 (2014) 24010-24014

ISSN: 2229-712X

5-SulphoSalicyclic Acid Mediated Expedious Synthesis of Bis (indolyl) methanes

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ARTICLE INFO

Article history:

Received: 17 November 2013;

Received in revised form:

25 November 2013;

Accepted: 29 November 2013;

Keywords

Sulphosalicyclic Acid,

Bis (indolyl) methanes,

Methanol.

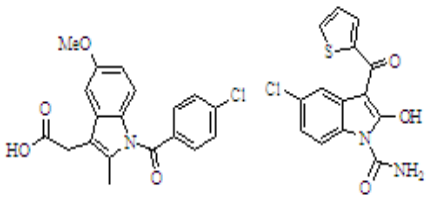
ABSTRACT

An expedious one pot, synthesis of bis (indolyl) methane was achieved in quantative yield, utilizing indole and substituted aromatic aldehyde using 5-SulphoSalicyclic Acid as a catalyst at room temperature within a short period of time.

Introduction

With a thrusting aim to develop environment benign reaction protocol, researchers are always in search for newer methods and techniques for facile organic transformation[1a]. With the same aim, we executed synthesis of bis (indolyl) methanes in our laboratory starting from Ionic liquids to nanomaterials and also utilizing grinding techniques[1b].

Although literature based on bis(indolyl) methanes synthesis is flooded with number of reports in the recent times but still there is scope and hope for development of better and convenient reaction protocol with green environment concept which can lead towards producing minimum amount of environmental waste. Besides having ecofriendly organic transformation concept in mind, researchers are interested in synthesizing *bis*(indolyl)methanes as it posseses numerous biological activity which includes anticancer[2], estrogen metabolism in humans[3], useful in the treatment of fibromyalgia[4], chronic fatigue[4], irritable bowel syndrome[4], highly selective fluorescent molecular sensors for Cu^{+2} ions[5], antioxidative[6], antibiotics[6], antimicrobial[8], cytotoxic[9], radical scavengers[10] antiviral[11], and insecticidal activities[12,] Further *natural bioactive indole*[13] derivatives mainly Indomethacin and Tenidap are shown to posses antiinflamatory, antipyretic and analgesic activities



Besides having novel biological activities in drug chemistry, they also shown to posses their significant mark in agrochemical[14] and material science[14] also. Thus regardless of its versatile biological and pharmacological activities, synthesis of *bis* (indolyl) methane and its derivatives has received notable attention in recent era days as there is continuous inflow of report for synthesizing these molecules in a view so that a novel, efficient synthetic method and procedures can be developed including various protic as well as Lewis acids[15].

Scheme 1 : 5-SulphoSalicyclic acid catalyzed synthesis of bisindolylmethanes

But as a matter of reaction it is observed that majority of synthetic methods have one or more demerits which involves use of toxic solvents, toxic metal reagent, tedious work up procedure, longer reaction time at higher temperature and finally may yield products in lower yields. Thus to bypass all these main drawbacks a novel, environmentally benign synthetic protocol is always in constant demand in the present scenario over a continuous time period.

Detailed literature survey confirms that so for very little work has been done utilizing 5-SulphoSalicyclic Acid[16] for carrying out reactions like, synthesis of Substituted Dihydropyrimidine-2(1H). So we thought of exploring 5-Sulfosalicylic acid's catalytic activity for performing organic transformation which is generally used for testing urine protein content[17] in urines colour anodizing[17] and also for the CAS assay to test for siderophore[17]. Thus to attain a general green synthetic approach towards obtaining synthesis of potent bioactive heterocyclic drug candidature entities for carrying out synthesis of bis(indolyl)methanes, we thought of recruiting 5-SulphoSalicyclic Acid catalyst to perform this transformation and also to study for its catalytic activity as the sea of reports is devoid of 5-SulphoSalicyclic Acid catalyst. So in this present paper we have developed a new protocol for the efficient synthesis of bis(indolyl)methanes from the corresponding aromatic aldehydes and indoles via the electrophilic substitution of indoles with different aromatic aldehydes using 5-SulphoSalicyclic Acid as a novel, ecofriendly, catalyst at room temperature.

Result and discussion:

The electrophilic substitution of indole with aromatic aldehyde is catalyzed by 5-SulphoSalicyclic Acid affording the product in excellent yield at room temperature. The reaction conditions on the reaction between indole and aldehydes are summarized in (Table 1).

Experimental Part

All the chemicals (AR grade) were purchased from SD fine chemicals and used without further purification. Melting points of the products were recorded using capillaries open at one end and were uncorrected. ^1H was recorded on 400 MHz Varian spectrophotometer in $CDCl_3$ solvent with TMS as an internal standard. IR was recorded on Bruker Vector 22 FTIR spectrophotometer using KBr discs.

Exact mass of the samples were recorded on Shimadzu mass analyzer. The progress of the reaction was monitored by Thin Layer Chromatography in 20 % ethyl acetate: hexane.

Typical procedure bis (indolyl) methane synthesis

In a typical model condensation reaction 5-SulphoSalicyclic Acid catalyst (10 mole %) was added to a mixture of aromatic aldehyde (10 mmol) and indole (20 mmol) dissolved in methanol. At the moment the catalyst is added, the reaction starts instantly, with change in color from colorless to colored viscous mass with sudden rise in the reaction temperature by few degrees. Further the resulting mixture was allowed to stir at ambidient temperature for around 30 minutes to complete the reaction. After completion of the reaction as indicated by TLC (20 % ethyl acetate: hexane) the reaction mass was diluted with methanol and after stirring for 5 minutes, the reaction mixture was poured onto the crushed ice. The separated mass was washed several times with water and the pure product was obtained by recrystallization from ethyl acetate and petroleum ether. All the products reported are known compounds and were identified by comparison with physical and spectral data of authentic samples from literature. The spectral data of selected compounds is described below:

Compound (2b): Brown solid, m.p. 209-211^oC , IR (KBr) cm^{-1} 3396, 3047, 2958, 2995, 1608, 1510, 1458, 1340, 1218, 1033; NMR (400 MHz $CDCl_3$) δ ppm 2.05(s, 6H), 3.8 (s, 3H), 5.95 (s, 1H), 6.8 (dd, 2H), 6.9 (dd,2H), 7.0 (m, 6H), 7.2(d, 2H), 7.73 (2H, br's, NH); ESMS 409 (M^+); Elemental analysis Cal. C=82.07, H=6.36, N=7.36, found C= 81.9, H= 6.089, N=7.02.

Compound (2c): Yellow solid, m.p. 241-243^oC, IR (KBr) cm^{-1} 3385, 3056, 2913, 2844, 1618, 1593, 1515, 1461, 1424, 1385, 1341, 1223, 852; ^1H NMR (400 MHz $CDCl_3$) δ ppm 2.09(s, 6H), 6.059 (s, 1H), 6.85-6.92 (m, 4H), 7.05 (d, 2H), 7.25 (d, 2H), 7.4(d, 2H), 7.83 (s, 2H), 8.1 (s, 2H) ESMS 395 (M^+); Elemental analysis Cal. C=75.93, H= 5.35, N= 10.63; found C=73.77, H=5.31, N=10.64.

Conclusion:

In short, an efficient synthesis of biologically valued *bis*(indolyl) methanes is achieved utilizing *5-SulphoSalicyclic acid* at room temperature in quantative yield, having unique features like short reaction time, simple experimental process, cleaner reaction protocol and easy isolation of products with no side products and utilization of environmental friendly, inexpensive catalyst, easily available, air stable, water-tolerant are the most promising and attractive features of this reaction protocol/methodology.

Acknowledgments:

We are sincerely thankful to Dr. M. L. Jadhav, Principal, Shri Muktanand College, Gangapur, Dist-Aurangabad (MS), India for his constant encouragement and providing us laboratory facilities during the work.

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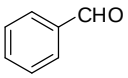
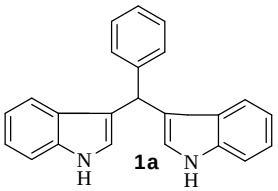
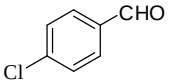
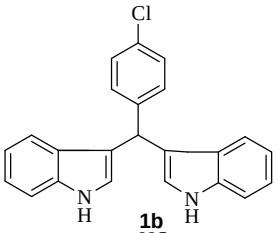
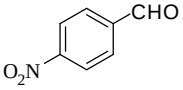
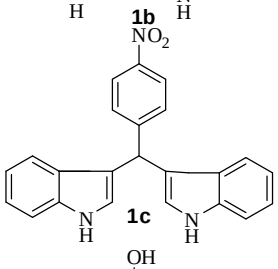
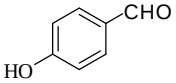
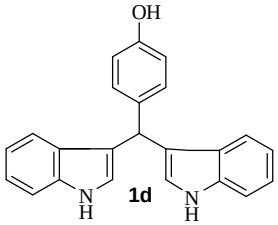
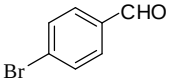
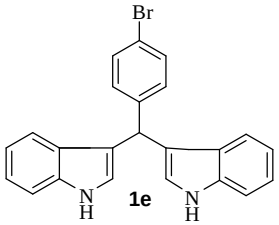
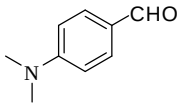
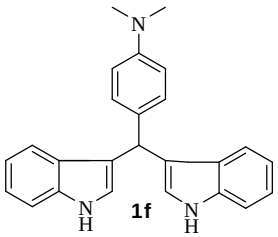
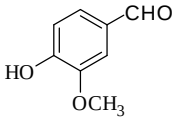
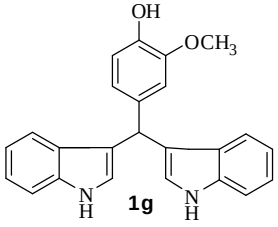
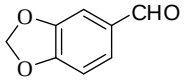
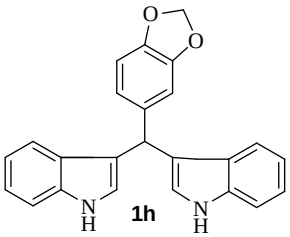
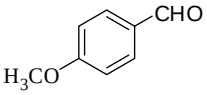
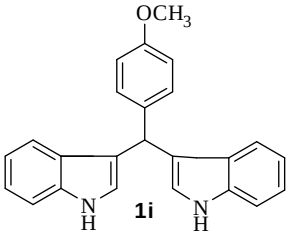
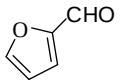
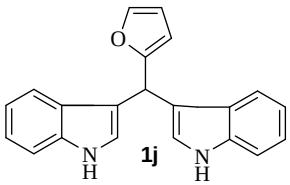
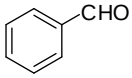
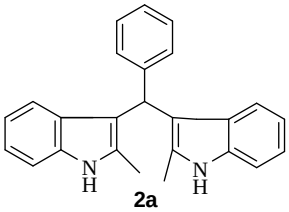
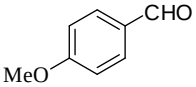
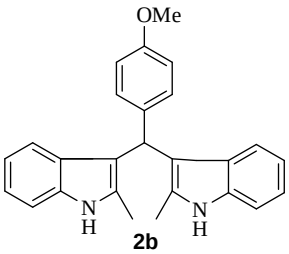
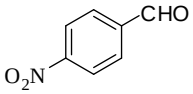
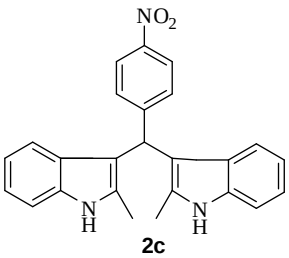
Table 1 *Yield and reaction time of 5-SulphoSalicyclic Acid catalyzed various bis(indolyl)methanes*

Entry	X	Aromatic Aldehyde	Product	Time (min)	Yield %	M. P. (°C)
1.	H		 **1a**	30	91	97-99[18]
2.	H		 **1b**	30	92	77-79[18]
3.	H		 **1c**	30	92	223-225[18]
4.	H		 **1d**	30	88	122-124[18]
5.	H		 **1e**	30	90	109-111[19]
6.	H		 **1f**	30	89	179-181[20]
7.	H		 **1g**	30	88	111-113[18]

Entry	X	Aromatic Aldehyde	Product	Time (min)	Yield %	M. P. (°C)
8.	H		 **1h**	30	86	88-90[18]
9.	H		 **1i**	30	92	189-191[18]
10.	H		 **1j**	30	83	320-322[18]
11.	Me		 **2a**	30	88	247-249[21]
12.	Me		 **2b**	30	90	209-211[22]
13.	Me		 **2c**	30	92	241-243[21]

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