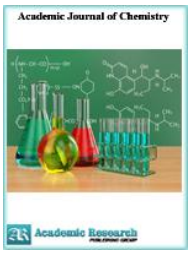

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Rapid Access to Synthesis of Bisindole Derivatives Using 2-Morpholino Ethanesulphonic Acid

Rajendra P. Pawar* Department of Chemistry, Deogiri College, Station Road, Aurangabad-431 005, MS, India

Devidas S. Bhagat Department of Forensic Chemistry, Government Institute of Forensic Science, Aurangabad-431004 MS, India

Suresh U. Shisodia Department of Chemistry, Deogiri College, Station Road, Aurangabad-431 005, MS, India

Hanuman D. Bhosale Department of Chemistry, Deogiri College, Station Road, Aurangabad-431 005, MS, India

Sudam S. Pandule Department of Chemistry, Nowrosjee Wadia College, Bund Garden Road, Pune 411001, MS, India

Pravin S. Kendrekar Department of Chemistry and Directorate: Research Development, University of the Free State, Nelson Mandela Drive 205, Bloemfontein 9301, South Africa

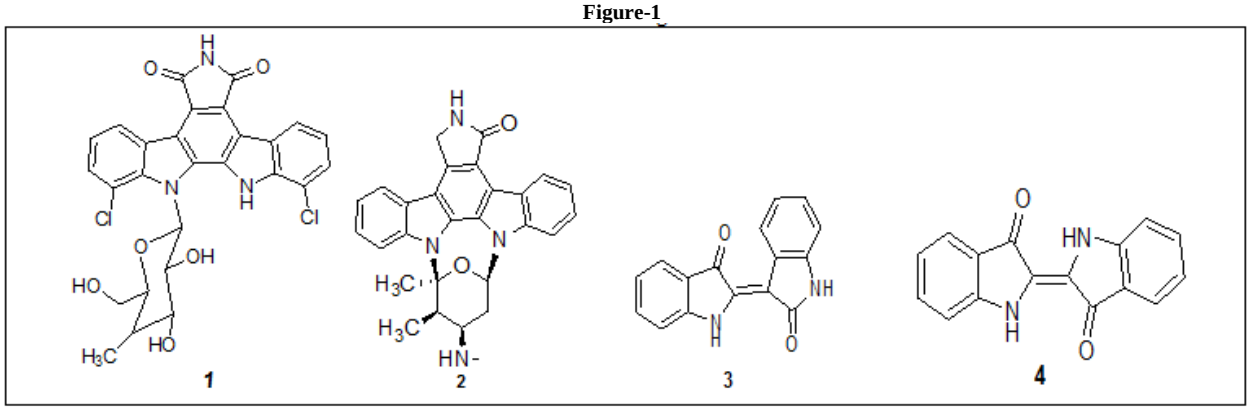
Abstract: The present work demonstrates easy and effective synthesis methodology for synthesis of bisindole derivatives in presence of protic organic acid 2-morpholino ethanesulphonic acid (MESA). 2-MESA is water soluble catalyst easy to extract and work-up for the synthesis of bisindole class of compounds. Catalyst is recovered and recycled by simple evaporation of water. Efficient aromatic electrophilic substitution of indoles (2 mmol) with aromatic aldehydes (1 mmol) equipped with various constituents were carried out employing a catalytic amount in ethanol to obtain bisindoles in good to excellent yields.

Keywords: 2-MESA (2-morpholino ethanesulphonic acid); Aldehyde; Bisindole; Green approach.

1. Introduction

Bisindole is a main subunit of many bioactive nitrogen containing heterocyclic compounds and natural products which were widely isolated from various plants terrestrial and marine natural sources [1]. Bisindole derivatives are widely found in nature and the chemistry of bisindole is one of the most interesting fields of research. Some natural products are rebeccamycine1, staurosporine2, Indirubin3 and indigotin4 (Figure-1) etc.

Figure-1



Bisindole derivatives have been the topic of interest from synthetic and biological point of view. The bisindole class of compounds has received excellent attention in past few decade since they possesses an excellent biological and pharmaceutical activities [2]. These various biological pharmacological activities are b-glycosidase inhibitory [3], KAR-2 on store-operated calcium entry in human neutrophils [4], a cytotoxic [5], anti-hyperlipidemic activities [6], anti-cancer chemopreventive agents [7], antiviral enantiomers [8], protein tyrosine phosphatase-1B inhibitory [9], antiviral glycosidic [10], breast cancer cell proliferation via SIRT-p53 axis [11], antineoplastic activity [12] etc.

Some representative examples of catalysts used for the synthesis of derivatives of bisindole are silica bonded S-sulfonic acid [13], SBA-15/SO_3H [14], Ph-PMO-SO_3H [15], vanado molybdo phosphoric acid [16], $Zn(HSO_4)_2$ [17]

*Corresponding Author

, CAN [18], acetic acid [19], sulphamic acid [20], silica sulfuric acid [21], Zirconium(IV) Chloride [22], $ZrOCl_2.8H_2O$ [23], *Citrus limon* Juice [24], iodine [1].

Scheme-1

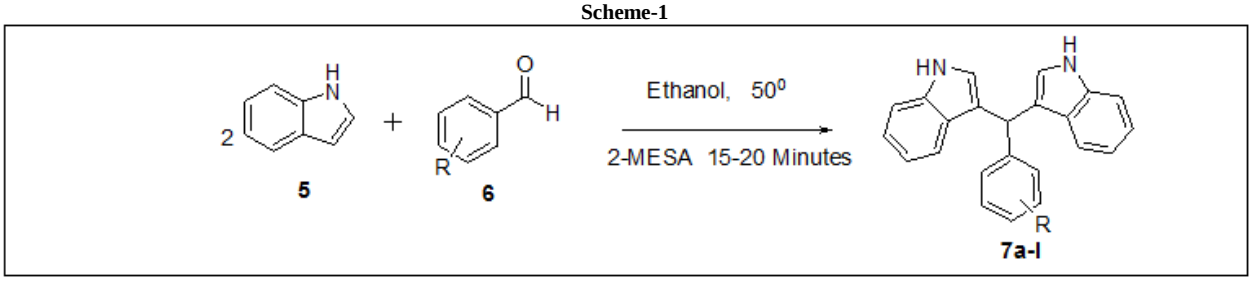


Table-1. Comparison of Catalyst and solvent on yield at different reaction condition

Sr. No.	Name of catalyst	Time (minutes)	Solvent	Temperature (O^0)	Yield (%)	Reference
1	silica sulfuric acid	40	--	RT	90	[21]
2	Zirconium (IV) Chloride	10	Acetonitrile	RT	90	[22]
3	$ZrOCl_2.8H_2O$	180	Ethanol	Ambient temperature	85-95	[23]
4	*Citrus limon* Juice	25	Ethanol	60	75-85	[24]
5	I_2	120	DMSO	80-90	60-70	[1]
6	2-MESA	10	Ethanol	50	95	Present work

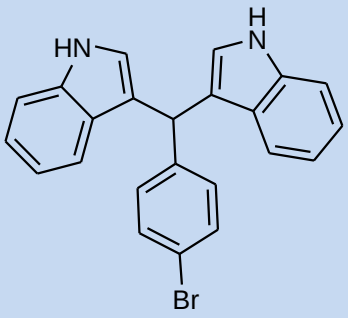
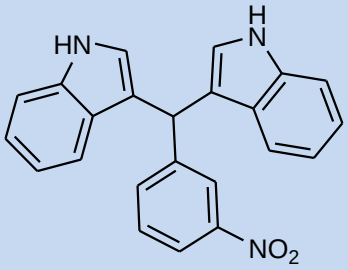
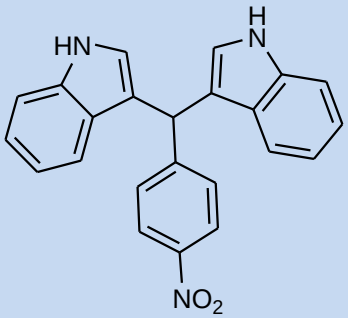
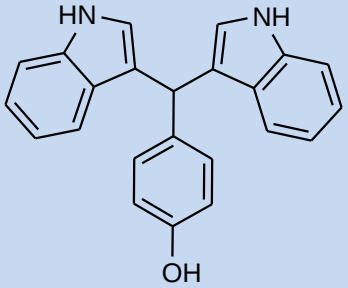
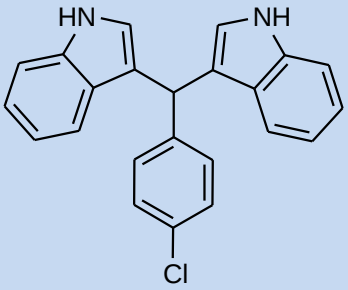
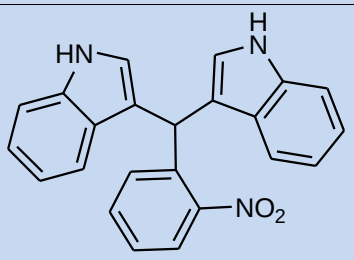
Table-2. Optimization of concentration of catalyst and Temperature

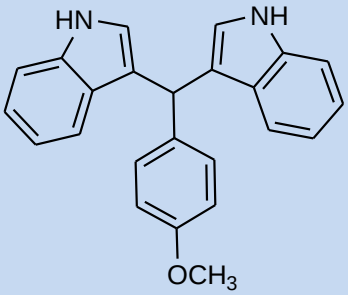
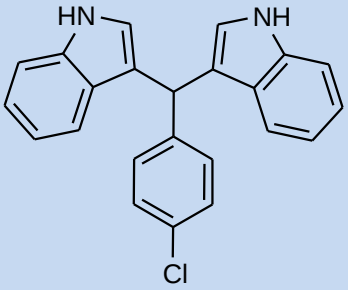
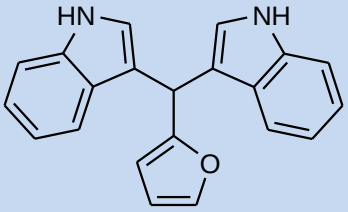
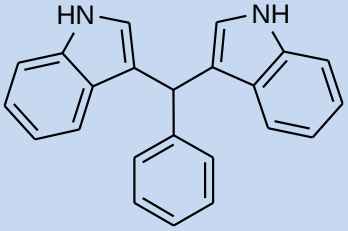
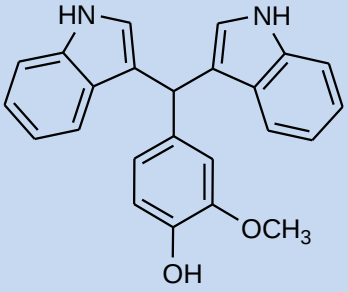
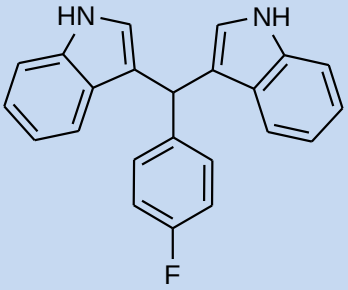
Sr. No.	2-MESA(mol%)	Temperature	Time (hr)	Yield (%)
1.	00	Reflux	15	Trace
2.	02	Reflux	5	50
3.	04	Reflux	4	55
4.	06	Reflux	3	65
5.	08	Reflux	2.5	70
6.	10	Reflux	1	80
7.	15	Reflux	10-15 minute	90-95
8.	20	Reflux	10-15 minutes	90-95
9.	15	RT	1-2 Hour	70
10.	15	40	1 hour	82
11.	15	78	10-20 minute	95
12.	15	60	10-20 minute	95

Table-3. Evaluation of Solvent for the synthesis of 7a-l at 50^0 C temperatures

Entry	Solvent	Time (hour/minute)	Temperature	Yield (%)
1.	Dichloromethane	2	Reflux	70
2.	Tetrahydrofuran	1	Reflux	75
3.	Tetrahydrofuran	1.5	Reflux	80
4.	Methanol	30 minutes	Reflux	85
5.	Acetonitrile	1	Reflux	80
6.	Dimethyl formamide	45 minutes	Reflux	70
7.	DMSO	1	Reflux	75
8.	Ethanol	10-15 minute	Reflux	90-95

Table-4. Synthesis of 3-((1H-indol-3-yl) (phenyl)methyl)-1H-indole derivatives

Entry	Synthesized compound	Time (minutes)	Yield (%)	Melting point ^{0}C	Reported Melting Point (^{0}C)	Reference Number
a.		10	92	110-112	108 - 111	[24]
b.		10	94	220-221	221-223	[22]
c.		10	95	263-265	264-265	[23]
d.		10	90	123-125	124-125	[22]
e.		10	91	115-118	120-122	[21]
f.		15	90	121-123	120-122	[23]

g.		20	92	182-184	178-181	[21]
h.		20	94	76-78	78-80	[23]
i.		20	90	318-320	321-322	[23]
j.		15	90	123-126	125-127	[21]
k.		15	95	113-115	111-112	[22]
l.		10	96	79-81	76-78	[23]

2. Materials and Methods

All the materials were of commercial grade reagent. Chemicals were purchased from Spectrochem and Sigma aldrich chemical companies in high purity, used without further purification. Melting points were determined in open capillaries using an Electrothermal Mk3 apparatus. Infrared (IR) spectra in KBr were recorded using a Perkin-Elmer FT-IR spectrometer 65. ^{1}H NMR spectra were recorded on 400 MHz FT-NMR spectrometer in $CDCl_3$ as a solvent and chemical shift values were recorded in δ (ppm) related to tetramethylsilane (Me_4Si) as an internal standard. The progress of the reactions were monitored on TLC (Thin Layer Chromatography).

3. Result and discussion

In search of the best experimental reaction conditions, we used 2-morpholino ethanesulphonic acid as a catalyst. An advantage of this catalyst is, it is water soluble. Thus, simply by filtration it goes in filtrate and on evaporation of water it is separated and reused in another reaction. In this process the use of hazardous organic solvents is minimized and helps in environment protection from pollutions. Whereas, most of the procedures developed for this reaction were reported by using hazardous organic solvents. Thus, that the process developed is greener as compare to the reported ones.

Initially, we optimized the reaction conditions with indole1 aromatic aldehyde 2 and considered as a model reaction (Scheme l). The effects of solvents, concentration of 2-MESA, and temperature were evaluated for this reaction, and the results are summarized in Table 2.and 3. When the reaction was carried out in absence of catalyst, the product formed in very trace amount (Table 2, entry 1). To evaluate the exact concentration of 2-morpholinoethanesulfonic acid required for the reaction, we investigated the model reaction (7a-i) using different concentrations (Table 2) such as "00, 02, 04, 06, 08, 10, 15 and 20 mol % the product was formed in 15, 50, 55, 65, 70, 80, 90-95 and 90-95% respectively". The result revealed that, when the reaction was carried out in presence of 00,02, 04, 06, mol % of catalyst, it gave lower yield of product even after prolonged time duration. While, using 10, and 15 mol % of catalyst afford excellent yield of products in short reaction time. The optimal results were obtained by using 15 mol % of catalyst and this concentration was ideal to carry out reaction smoothly (Table 2, entry 7); making it the most favorable solvent. However, initiation of the reaction was not observed even after 1 hour and thus starting materials were quantitatively recovered. This study revealed that, in presence of 2-MESA, aromatic aldehyde react with indole to give e the desired product. In evaluations of temperature the reaction was carried out at RT, 40, 50 and 60 ^{0}C; the yield of product obtained for this temperature are 70, 82, 95 and 90 % respectively. It was found that in presence of 2-MESA an excellent yield of product formation is takes place at 50 ^{0}C. Futher, an increase in temperature was not affect the yield and time of reaction (Table-2). To establish the optimum experimental conditions to obtain best yield of product 3-((1H-indol-3-yl)(phenyl)methyl)-1H-indole derivatives, different aromatic aldehyde were treated with indole in presence of 15 mole % 2-MESA using ethanol as a solvent at 50 ^{0}C temperature. The 2-MESA is better catalyst gives excellent yield of products at 50 ^{0}C as compared to other catalyst (Table-1). Notably, all the substrates were observed to be well tolerated under optimized conditions furnishing the product.

3.1. General Procedure for the Synthesis of 3-((1H-Indol-3-Yl)(Phenyl)Methyl)-1H-Indole Derivatives

In 25 mL round bottom flask a mixture of aromatic aldehydes (1 mmol), indole (2 mmol) and catalyst 2-MESA 15 mole%, in ethanol (5 mL) was refluxed for appropriated time (Table 4**)**. The progress of reaction was monitored by TLC. On completion of reaction, the mixture was cooled to room temperature; the content was filtered and washed with water to remove because catalyst. The separated solid was recrystalized in ethanol to afford the pure 3-((1H-indol-3-yl)(phenyl)methyl)-1H-indole. The filtrate was evaporated and the separated catalyst was reused in IInd cycle of reaction. 3-((4bromophenyl)(1H-indol-3-yl)methyl)-1H-indole

3.2. Spectral Analysis of Some Derivatives

4a. 3-((4bromophenyl)(1H-indol-3-yl)methyl)-1H-indole

Pale Yellow solid; yield 92%; mp 110-112°C; Recrystallised in Ethanol; NMR (**$CDCl_3$)** 5.8 (s, 1H), 6.7 (s, 2H), 6.9 (d, 2H) 7.2 (m, 4H), 7.5 (m, 4H), 10.5 (d, 2H)∂(ppm).

4b. 3-((1H-indol-3-yl)(4nitrophenyl)methyl)-1H-indole

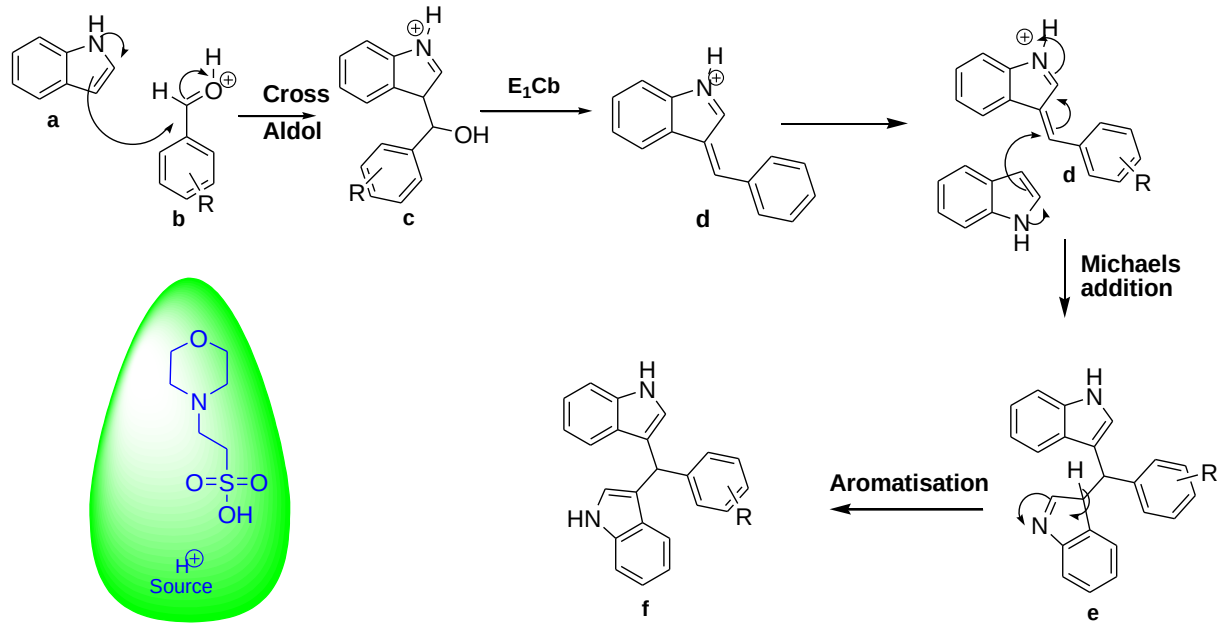
Pale Yellow solid; yield 94%; mp 220-221°C; Recrystallised in Ethanol; NMR (**$CDCl_3$)** 5.85 (s, 1H), 6.8 (s, 2H), 6.9 (d, 2H), 7.0 (d,2H) 7.1 (m, 4H), 7.5 (m,4H), 10.5 (d, 2H)∂ (ppm).

4c. 3-((1H-indol-3-yl)(3nitrophenyl)methyl)-1H-indole

Pale Yellow solid; yield 95%; mp 263-265°C; Recrystallised in Ethanol; NMR (**$CDCl_3$)** 6.0 (s, 1H), 6.7 (s, 2H), 6.9 (m, 2H), 7.0 (m,2H) 7.2-7.3 (m, 4H), 7.7 (m,1H), 7.8 (m, 1H), 8.00 (d,1H), 8.2(d,1H) 7.5, 10.7 (d, 2H)∂ (ppm).

4. Reaction Mechanism

In this reaction 2-MESA acts as Bronsted acid (proton donner) [25], and increase the electrophilicity of carbonyl carbon of aldehyde. In reaction mechanism **a** on cross Aldol condensation with **b** gave intermediate **c;** it on E1cb elimination gives intermediate **d**. The **d** on Michael addition gives intermediate **e**, which on rearrangement gives **f** 3-((1H-indol-3-yl)(phenyl)methyl)-1H-indole derivatives.



5. Conclusion

In summary, we have developed an efficient way to synthesize bis(indolyl)methane derivatives using 2-MESA. It acts as excellent catalyst for this greener synthesis due to its water solubility and easy extraction work up. Simply by evaporation of water the catalyst can be reuse and recycled, making this methodology efficient, convenient, rapid and eco-friendly. This method is an environmentally benign, efficient required shorter reaction time and simple work-up procedures.

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