



Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Simple and efficient synthesis of bis(indolyl)methanes by using $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$

Vishvanath D. Patil*, Nagesh R. Sutar and Ketan P. Patil

Organic Chemistry Research Laboratory, Department of Chemistry, C. K. Thakur A.C.S. College New Panvel,
Raigad, Maharashtra, India

ABSTRACT

Biologically active Bis(indolyl)methanes have been synthesized by using $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ as a catalyst in $\text{C}_2\text{H}_5\text{OH}$ at room temperature. $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ in $\text{C}_2\text{H}_5\text{OH}$ was found to be an efficient, moisture tolerant and reusable catalyst in reaction of indole with different carbonyl compounds giving corresponding derivatives of Bis(indolyl)methanes. The attractive features of this protocol involve mild reaction condition, excellent yields, simple work up procedure and recyclability of catalyst.

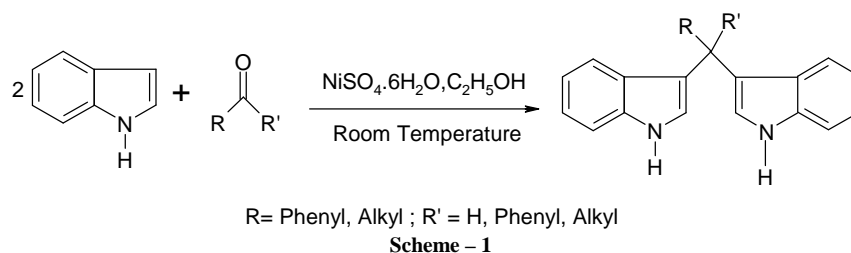
Keywords: room temperature; reusable catalyst; mild; excellent yields.

INTRODUCTION

There is need to develop simple, efficient & economically viable chemical pathways to synthesize biologically active & commercially important Bis(indolyl) methanes [1]. The indole ring is an important constituent of many natural products, pharmaceuticals & other compounds of commercial importance [2]. The literature survey shows that Bis(indolyl) methanes are known to increase estrogen metabolism in human beings and hence can be used for the treatment of breast cancer, it also exhibits antibacterial activities[3-5]. This wide range of applications has encouraged the chemists to develop new methods to synthesize Bis(indolyl)methanes.

Accordingly, different methods have been developed for the synthesis of Bis(indolyl)methanes using Lewis acid catalysts such as LiClO_4 [6], $\text{In}(\text{oTf})_x$ and InCl_3 [7-8], $\text{Sc}(\text{OTf})_3$ [9], molecular iodine [11], Zr(IV)Chloride [12], CuBr_2 [13]. Some protocols involve use of ionic liquids [14-15], trichloro-1, 3, 5-triazine [16], potassium hydrogen sulphate [17], ceric ammonium nitrate [18] and sulphamic acid [19]. However, these reported protocols suffer from one or other disadvantages such as harsh reaction conditions, low yields and use of reagents which are costly, sensitive to moisture. So there is need of development of a mild and efficient methodology for the synthesis of Bis(indolyl)methanes.

In this communication, we report a synthesis of Bis(indolyl)methanes by using $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ in $\text{C}_2\text{H}_5\text{OH}$ as a catalyst. The mentioned catalyst was found to be efficient in formation of Bis(indolyl)methanes by one pot two component reaction of carbonyl compound and indole. Moreover, used catalyst $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ was found to be stable towards moisture and recyclable one (Scheme-1).



EXPERIMENTAL SECTION

All chemicals and solvents were procured from Sigma-Aldrich, Merck and used without any further purification. Melting points were determined using an open capillary apparatus and used without correction. All ¹H NMR spectra were recorded on 200 and 300 MHz Bruker-Avance FT-NMR spectrometer. All chemical shifts were given as δ values with reference to Tetramethyl silane (TMS, $\delta=0$) as an internal standard and expressed in terms of parts per million (ppm). IR spectra were recorded on Perkin-Elmer FT IR spectrometer as KBr pellets.

General Experimental Procedure for the synthesis of Bis(Indolyl)methanes:

A mixture of carbonyl compound (1 mmol), Indole (0.234 gm, 2 mmol) and NiSO₄.6H₂O (0.026 gm, 0.1 mmol) in C₂H₅OH was stirred magnetically at room temperature. The progress of the reaction was monitored by thin-layer chromatography using 5 x 20 cm aluminum foiled silica gel coated plates (Brand-Merck) with petroleum ether and ethyl acetate (9:1) as solvent system. After completion of reaction as indicated by TLC, chloroform (3.0 ml) was added to reaction mixture and it was filtered to separate catalyst. The combined filtrate was evaporated under reduced pressure to get product which was purified by column chromatography using silica gel (60-120 mesh) and combination of petroleum ether and ethyl acetate (9:1) as solvent system. The separated catalyst was further washed with chloroform and reused for the same set of reactions. It was observed that the catalyst could be recycled for at least three cycles without much loss in catalytic activity. The synthesized Bis(indolyl)methanes were known compounds. The melting point data of all Bis(indolyl)methanes was compared with data available in literature and thus confirmed the formation of desired products (Table 4.). Further, the derivatives of Bis(indolyl)methane were analyzed by IR and ¹H NMR.

Spectral data of selected Bis(Indolyl)methanes

Phenyl- 3, 3'-bis (indolyl) methane (1b)

IR (KBr): 429, 529, 586, 601, 736, 822, 928, 1012, 1095, 1340, 1456, 2927, 2957, 3382 cm⁻¹

¹H NMR (300MHz, CDCl₃): δ =5.82(s, 1H), 6.45(s, 2H), 6.85-7.25(m, 5H), 7.25-7.40(m, 8H), 7.78(br, s, 2H, 2X NH)

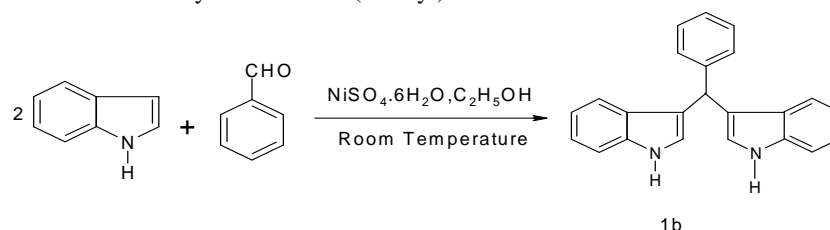
4-nitrophenyl -3, 3' bis (indolyl) methane (5b)

IR (KBr) = 426, 745, 1010, 1093, 1221, 1339, 1455, 1507, 2922, 3052, 3386, 3422 cm⁻¹

¹H NMR (CDCl₃, 300MHz) δ = 6.11(s, 1H), 6.81(s, 2H), 7.11(d, J=7.5Hz, 2H), 7.25(d, J=7.5Hz, 2H), 7.45-7.55(m, 8H), 8.12(br, s, 2H, 2X NH)

RESULTS AND DISCUSSION

The reaction proceeded efficiently and smoothly at room temperature in presence of NiSO₄.6H₂O as a catalyst in C₂H₅OH. The products were obtained in good to excellent yields. The optimization of the reaction condition was done by selecting the reaction between indole (0.234 gm, 2 mmol) and benzaldehyde (0.101 ml, 1mmol) as a model reaction (Scheme 2). It was performed in different solvents. The solvents with low polarity gave corresponding product in long reaction time with low yield (Table 1, Entries 1, 2, 3). On the other hand, C₂H₅OH, a polar solvent, gave corresponding product in short reaction time with excellent yield (Table 1, Entry 4). So C₂H₅OH was selected as most appropriate solvent for the synthesis of Bis(indolyl)methanes.



Scheme-2

Table 1. Effect of solvent on reaction of indole with benzaldehyde in presence of NiSO₄.6H₂O

Entry	Solvent	Time (min.)	Yield ^a (%)
1	CH ₂ Cl ₂	80	30
2	CHCl ₃	65	40
3	CH ₃ CN	60	45
4	C ₂ H ₅ OH	10	96

^aIsolated Yield (%)

Similarly, the catalytic activity of NiSO₄.6H₂O was investigated with respect to its loading amount.

Table 2. Study of catalytic activity of NiSO₄.6H₂O with respect to its loading amount

Entry	NiSO ₄ .6H ₂ O (mmol)	Time (min.)	Yield ^b (%)
1	0.01	40	50
2	0.05	35	55
3	0.1	10	96
4	0.2	10	96

^bIsolated Yield (%)

The yield of corresponding Bis(indolyl)methane in model reaction was maximum when 0.1 mmol (0.026 gm) of NiSO₄.6H₂O was used as catalyst (Table 2, Entry 3). There was hardly any improvement in results when 0.2 mmol of NiSO₄.6H₂O was used as catalyst.

The heterogeneous nature of NiSO₄.6H₂O in reaction medium encouraged was checking its reusability. The easily recovered catalyst was used to synthesize corresponding Bis(indolyl)methane from fresh indole and benzaldehyde in C₂H₅OH. The catalyst could afford the corresponding product for at least three runs without much loss in its catalytic activity as shown in Table 3.

Table 3. Study of reusability of NiSO₄.6H₂O in the synthesis of Bis(indolyl)methanes

Run No.	1	2	3
Time (min.)	10	30	35
Yield ^c (%)	96	90	86

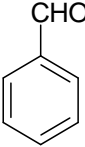
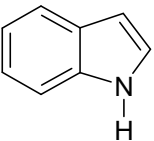
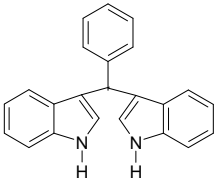
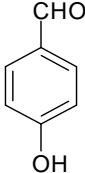
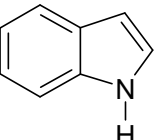
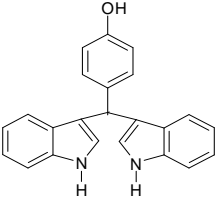
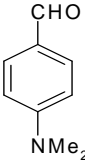
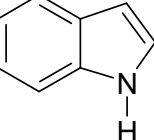
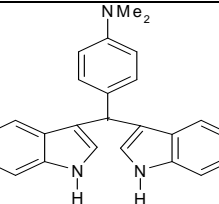
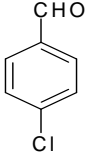
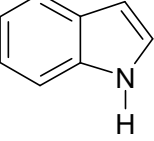
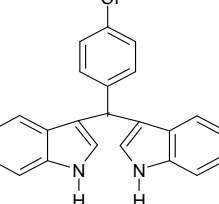
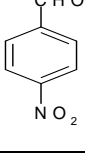
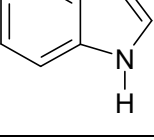
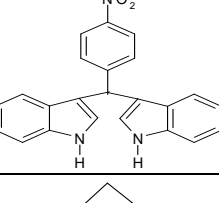
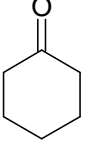
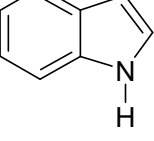
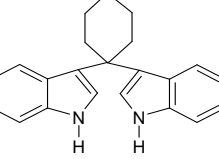
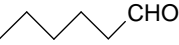
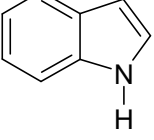
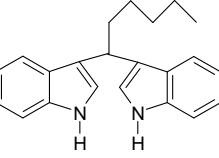
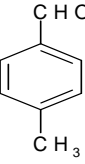
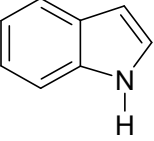
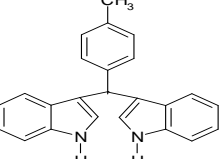
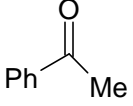
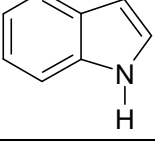
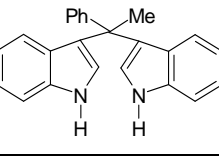
^cIsolated Yield (%)

Thus, NiSO₄.6H₂O was proved to be a heterogeneous, recyclable and efficient catalyst for the synthesis of Bis(indolyl)methanes from indole and various carbonyl compounds.

In order to show general nature and wide scope of this method, various aldehydes & ketones were made to react with two equivalents of indole under same reaction condition. It was found that the reaction occurs smoothly giving excellent yields in short reaction time (Table 4, Entries 1-9).

During study, it was observed that aromatic aldehydes reacted smoothly as compare to ketones (Table 4, Entries 6, 9). In case of substituted aromatic aldehydes, those with electron donating substituents reacted in short reaction time giving maximum yields (Table 4, Entries 2, 3, 4, 8). On the other hand, those aromatic aldehydes with electron withdrawing substituents required more reaction time to form corresponding product with comparable yield (Table 4 Entry 5).

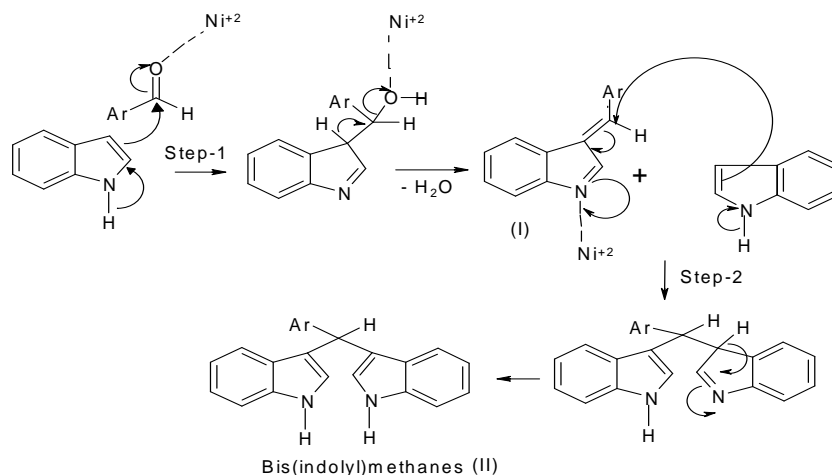
Table 4. Synthesis of Bis(indolyl)methanes from indole and carbonyl compounds

Entry	Aldehyde ^a	Indole	Product ^b	Time (min)	Yield ^c (%)	M.P.(^o C) (Literature Value)
1				10	96	124-127 ^o C (125-126 ^o C) ^{10b}
2				10	93	121-123 ^o C (122-124 ^o C) ¹⁸
3				15	91	94 ^o C (92-95 ^o C) ¹⁹
4				15	92	103-106 ^o C (104-105 ^o C) ¹⁶
5				25	88	262-266 ^o C (265-266 ^o C) ¹⁷
6				25	88	117-119 ^o C (118-120 ^o C) ⁶
7				20	86	66-69 ^o C (68-70 ^o C) ⁶
8				15	94	96-98 ^o C (95-97 ^o C) ⁶
9				30	89	188-190 ^o C (189-190 ^o C) ²⁰

^a The substrate was treated with Indole (2 mmol) by stirring at room temperature with NiSO₄.6H₂O in presence of C₂H₅OH as solvent;

^b All products were identified by their melting points, IR and ¹H NMR spectra; ^c Isolated yields (%).

The Scheme 3 depicts the plausible mechanism for the reaction between 2 moles of indole and 1 mole of aromatic aldehyde in presence of NiSO_4 (a source of Ni^{+2} as Lewis acid). Thus, overall mechanism is aromatic electrophilic substitution reaction of indole with aromatic aldehyde in presence of Ni^{+2} salt as Lewis acid catalyst [20, 21]. The reaction proceeds through activation of carbonyl compound by coordination with Ni^{+2} , a Lewis acid (Step-1) followed by formation of an aza fulvenium intermediate (I). The formed intermediate gets activated through coordination with Ni^{+2} and adds second molecule of indole (Step-2). The rearrangement involving proton shift gives final product (II).



Scheme 3

CONCLUSION

Thus, $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ in $\text{C}_2\text{H}_5\text{OH}$ was found to be an efficient and reusable catalyst for the synthesis of Bis(indolyl)methanes from different carbonyl compounds and indole. The mild reaction condition, simple work up procedure, good to excellent yields and use of reusable catalyst makes this method as one of the best synthetic pathways available for preparation of Bis(indolyl)methanes.

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