Synthesis of bis(indolyl)methane using tetrabutyl ammonium hydrogen sulphate in aqueous medium- Green approach

[1]Harindran Suhana, [2]Premkumar.G

Dept. of Chemistry, SRM University, Kattankulathur-603203, Tamil Nadu, INDIA
Email: suhana.h@ktr.srmuniv.ac.in

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Abstract: We herein report a green approach synthesis of bis(indolyl)methanes by reacting indole with a series of aromatic aldehydes using an environment friendly catalyst tetrabutyl ammonium hydrogen sulphate in aqueous medium. A survey of literature revealed that these compounds have been prepared by reaction between indole and carbonyl compounds, generally aldehydes or ketones in organic solvents in the presence of acid catalysts. However these methods suffer from several disadvantages such as long reaction time, low yield of product, expensive catalyst, harsh reaction conditions, cumbersome workup procedure and environmentally toxic reagents. The best features in our method are clean reaction conditions, simple workup procedure, short reaction time and easy isolation of product. The products are obtained in high yields and have been characterized by IR and ^{1}H NMR spectra.

Keywords: Bis Indolyl methane, Green approach, chemo sensor, ^{1}HNMR

I. INTRODUCTION

Bis(indolyl)methanes which contain two indole or substituted indole units in a molecule are an important group of bioactive metabolites[1-4] of terrestrial and marine origin. They are an important class of bioactive cruciferous ingredients responsible for promoting beneficial estrogen metabolism in men and women, radical inhibitors for human prostate cancer cell, radical scavengers, antiviral agents and exhibit photophysical properties. The oxidized form of bis(indoly)methane are utilized as dyes as well as colorimetric chemosensors.

The first report on synthesis of bis(indolyl)methanes was in 1886, when Fischer prepared them by acid catalyzed Friedel-Crafts reaction between indole and carbonyl compounds.

Sujatha[5] et al have synthesized a series of these compounds by stirring a mixture of indole and aldehyde in methanol:water(1:1) containing catalytic amount of sodium bisulphate at room temperature.

Sarita Mishra[6] et al described an ecofriendly and efficient synthesis by reacting indole with aldehyde using camphor sulfonic acid or $ZrOCl_2.8H_2O$ as catalyst in 20% ethanol -water mixture at ambient temperature.

H.M. Meshram [7] et al reported a boric acid promoted convenient synthesis of bis(indolyl)methanes in aqueous medium in high yield.

V.Jhansi Rani [8] et al reported a PEG-SO_3H catalysed synthesis by reaction of indole with aldehyde in aqueous medium.

B.Y.Giri [9] et al reported a mild and efficient synthesis of these compounds using monoammonium salt of 12-tungstophosphoric acid in acetonitrile at room temperature.

An efficient synthesis has been reported by D.R.Chandam [10] et al under solvent free conditions using silica supported chloro acetic acid as reusable catalyst .

Reaction of substituted indole with aldehydes using ethyl ammonium nitrate as ionic liquid was reported by Shaffek. A [11] et al.

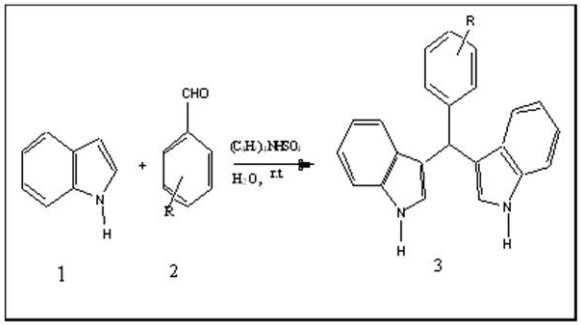
Frahad Shirini [12] et al reported an efficient synthesis of bis(indolyl)methanes catalyzed by N-sulfonic acid poly(4-vinylpyridinium)chloride under solvent free conditions at room temperature.

Green approach synthesis of the target molecule has been reported by K..Harshavardhan Reddy [13] et al under solvent free and catalyst free conditions at room temperature.Another method was reported by A.Rajendran [14] et al using ionic liquid triethylammonium hydrogen sulphate.

Mohammed Zamir Ahmed [15] et al employed a natural approach of lemon juice catalysed condensation of indole with aldehyde..

II. RESULTS AND DISCUSSION

In general many synthetic protocols have been developed for the synthesis of bis indolyl methanes. However all the methods reported so far have many limitations such as expensive reagents, drastic reaction conditions, toxic and flammable organic solvents, high reaction time and complicated workup procedure. We have developed a convenient and environmentally green methodology for the synthesis of bis (indolyl) methanes in the absence of hazardous solvents.



Scheme: 1 Synthesis of bis(indolyl)methanes

Table-1: Yield and Melting Point of the compounds (1-6)

Entry	1 Synthesis of bis(indolyl)methanes			
	Indole	Aryl aldehyde (2a-g)	Yield % (3a-f)	M.pt(0C) (3a-f)
1			92	124-128
2			93	104-105
3			90	120-121
4			94	220-221
5			89	191-193
6			85	196-198

The compounds (3a-f) have been synthesized and analyzed by ^{1}H NMR and IR spectra.

The above reaction failed when extended to fused aromatic ring systems such as anthraldehyde. Even aromatic ketones such as acetophenone and benzophenone failed to give the desired product. In all cases the starting materials was recovered.

The optimized reaction conditions were screened by different amounts of the catalyst under aqueous conditions.

The results are summarized in Table-2

Table-2: Optimization of reaction conditions

Entry	Catalyst amount	Reaction time	Yield%
1	10 mmol	Overnight	40
2	20mmol	5 h	40
3	50mmol	1-1.5 h	60
4	2 equivalent	0.5 h	92

First the reaction was done overnight and resulted in low yield of the product. It was found that an increase in the amount of catalyst decreased the reaction time and increased the yield. The optimization was done with 4-chlorobenzaldehyde.

Moreover the scope and efficiency of the catalyst was explored under the optimized reaction conditions. For this purpose, indole was condensed with abroad range of structurally and electronically diverse aromatic aldehydes to produce the corresponding bis(indolyl)methane in high yield and short reaction time.

The influence of electron withdrawing and electron releasing substituents on the aromatic ring of aldehydes upon reaction yields was investigated. The results showed that the reaction times slightly decreased but the yield increased in presence of electron withdrawing groups. However electron releasing groups in para and ortho position of aromatic aldehydes decreased the yield of the product. This is attributed to the fact that electron releasing groups decrease the electrophilic character of the carbonyl carbon.

III. EXPERIMENTAL

The required chemicals were purchased from S.D. fine chemicals (India). Melting points were determined by an open capillary method and are uncorrected. The IR spectra were recorded on Shimadzu FT-IR 157 spectrophotometer. ^{1}H NMR spectra were recorded using $CDCl_3$ or DMSO-d_6 as solvent and TMS as an internal standard on Brucker 500 MHz spectrophotometer. The chemical shift values are expressed in part per million (ppm).

General procedure for the synthesis of bis(indolyl)methanes (3a-g)

A mixture of indole (2mmol) and aldehyde(1mmol) in 20 ml of water was stirred thoroughly using a magnetic stirrer for 30 minutes in the presence of tetrabutylammonium hydrogen sulphate(2mmol).The reaction was monitored by thin layer chromatography. After completion of the reaction, the reaction mixture was diluted with water. It was then extracted with ethyl acetate (2x20ml). The combined organic extract was dried over Na_2S0_4, filtered and solvent removed. Purification by column chromatography furnished the desired bis(indolyl)methane.

3, 3'- Bis(indolyl)phenyl methane (Entry 1, 3a)

IR (KBr) cm^{-1}: 3450, 3020, 1600, 1490, 1220, 1070, 750
^1H NMR ($CDCl_3$, 500 MHz): 5.85(s, 1H,CH), 6.50-6.60(d,2H,J=2.4Hz), 7.00-7.10(t, 2H, J=8.2Hz), 7.15-7.25(t, 2H, J=8.2Hz),7.30-7.50(m, 9H, Ar-H), 7.75-7.85(brs, 2H, NH)

3, 3'-Bis(indolyl)(4-chlorophenyl)methane (Entry 2, 3b)
IR cm^{-1}: 3411,3055, 1617,1417,1337,1089,1013,743
^1H NMR (500MHz,$CDCl_3$): 5.80(s, 1H, CH), 6.55-6.65(d, 2H, J=2.4Hz), 7.00-7.10(t, 2H, J=7.8Hz), 7.15-7.20(t, 2H, J=7.8Hz), 7.25-7.40(m, 8H, Ar-H), 7.85(s,br, 2H, NH)
3,3'-bis(indolyl)(4-hydroxyphenyl) methane (Entry 3,3c)
IR (KBr)cm^{-1}:3441,1632,1166,746
^1H NMR ($CDCl_3$, 500 MHz):4.85(s, 1H, OH), 5.85(s, 1H, CH), 6.65(d, 2H), 6.85-6.90(t, 2H, J=1.6Hz), 6.95-7.00(d, 2H, J=7.6Hz), 7.05-7.15(m, 3H, Ar-H), 7.20-7.25(d, 2H, J=7.6Hz),7.30-7.35(m, 3H, Ar-H),10.15(s, br, 2H, NH)

3, 3´-Bis(indolyl)-4-nitrophenyl methane (Entry 4, 3d)
IR (KBr) cm^{-1}: 3420, 3050, 1595, 1510, 1455, 1340, 1086,736
^1H NMR ($CDCl_3$, 500 MHz): 5.98(s, 1H, CH), 6.65-6.75(d, 2H, J=2.4Hz), 6.80-6.95(t, 2H), 7.05-7.15(t, 2H), 7.20-7.25(d, 2H,J=8.1Hz), 7.35-7.40(d, 2H,J=8.1Hz), 7.50-7.60(d, 2H,J=8.Hz) 8.05-8.10(d, 2H, J=8Hz) 10.45(s, br, 2H,NH)

3,3´-Bis(indolyl)-4-hydroxyphenyl methane (Entry 5, 3e)
IR (KBr) cm^{-1}:3441, 1632,1166,746
^{1}HNMR($CDCl_3$,500MHz):4.85(s,1H,OH),5.85(s,1H,CH) ,6.65(d,2H),6.85-6.90(t,2H,J=1.6Hz),6.95-7.00(d,2H,J=7.6Hz),7.05-7.15(m,3H,Ar-H),7.20-7.25(d,2H,J=7.6Hz)7.30-7.35(m,3H,Ar-H),10.15(s,br,2H,NH)

3, 3'-bis(indolyl)-[(3,4dimethoxyphenyl)methane(Entry 6 , 3f)

IR (KBr)cm-1: 3450,3060,1620,1490,1230,1005,750

^1H NMR ($CDCl_3$, 500MHz) δ 3.75(s, 3H, -OMe), 3.85 (s, 3H, -OMe), 5.75(s, 1H,-CH), 6.65-6.75 (s,2H, J=2.4Hz), 6.75-6.85(d,2H,J=8Hz) 6.85(s,1H),6.90-7.00(d,2H,J=8Hz), 7.05-7.15(t,2H,J=8Hz),7.30-7.40(t,4H,J=8Hz), ,7.90(s,br,2H,NH)

IV .CONCLUSION

In short we have developed a highly efficient and convenient method for the synthesis of bis(indolyl)methane using inexpensive and environment friendly catalyst tetrabutylammonium hydrogen sulphate in aqueous medium.

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