



AN EFFICIENT SYNTHESIS OF BIS (INDOLYL) METHANES USING TARTARIC ACID CATALYST

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Abstract: Tartaric acid was found to be a mild, efficient acid catalyst in electrophilic substitution reaction of indoles with carbonyl compounds to afford the corresponding bis(indolyl)alkanes in excellent yields. In the present work, various electrophilic substitution reactions of indoles with several aldehydes were carried out. Superiority of the present method is the mild reaction conditions, short reaction times, easy work-up, high to excellent yields, The optimal reaction conditions were fixed and the products were characterized by FT-IR, ¹H-NMR.

Keywords: Tartaric acid, Indole, Aromatic Aldehyde, bis (indolyl) methanes, Spectral analysis.

Introduction

The bis(indolyl)methanes have been gaining increasing importance in recent years and known as an important class of heterocyclic compounds. These types of compounds are also known to promote the estrogen metabolism in both women and men and are expected to have an application in prevention of breast cancer^{i,ii} Bis(indolyl)methanes (BIMs) also exhibit a range of biological activities such as antimicrobial and antifungal, antibacterial, analgesic and anti-inflammatory, growth promoting ,antitumoractivitiesⁱⁱⁱ

A wide range of pharmaceutical applications of bis(indolyl)methane derivatives has grown interest among chemist to develop their easy synthetic methods.A simple, standard and common method for the synthesis of bis(indolyl)methanes is the Friedel–Crafts reaction between indoles and carbonyl compounds in the presence of protic acids or lewis acids. Varieties of catalytic reagents used in the synthesis of BIMs have been reviewed. Researchers are competing for developing the economic, eco-friendly, easily accessible methodologies for the synthesis of bis (indolyl) methane by using various catalytic systems and reaction conditions like citrus lemon juice^{iv} grapejuice^v phenylphosphonicacid^{vi} triethylborane^{vii} poly (4-vinylpyridinium) hydrogensulfate^{viii},tetrabutyl ammonium hydrogen sulphate^{ix}, Silica

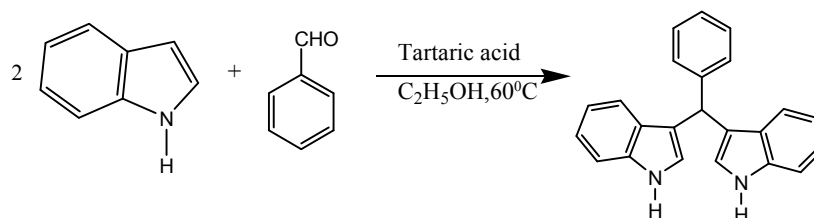
supported chloroacetic acid^x silica gel under microwave irradiation^{xi} AgOTf^{xii} Alum (KAl(SO₄)₂·12H₂O)^{xiii}, palladium nanoparticles^{xiv} nanosilica gel^{xv} P₂O₅/SiO₂^{xvi}, PS-AlCl₃^{xvii}

Most of these reported methods suffer from one or several drawbacks, including the requirement of large or stoichiometric amount of catalysts, low yields, prolonged reaction times, involving harsh reaction conditions, tedious workup procedure, and difficulty in recovery, expensive catalysts.

In this report we have investigated the synthesis of various bis (indolyl) methanes catalyzed by tartaric acid.

Result and Discussion

We presented here the methodology for the synthesis of bis (indolyl) methanes employing easily available tartaric acid catalyst. The reaction was carried out within a short period of time. The optimized reaction conditions were screened by different amounts of the catalyst in ethanol solvent. (Scheme-1)



Scheme-1: synthesis of bis (indolyl) methanes using acid catalyst

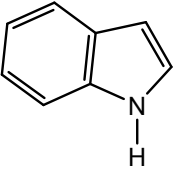
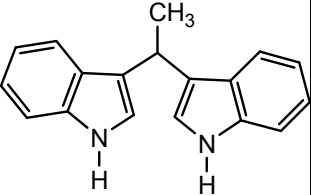
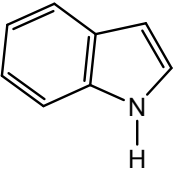
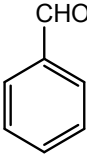
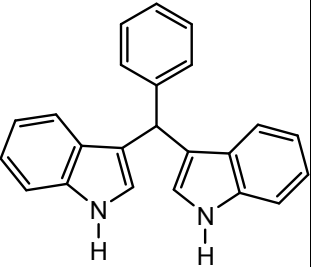
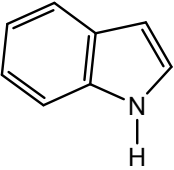
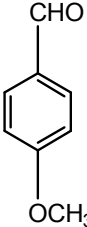
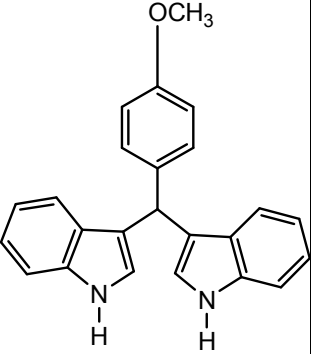
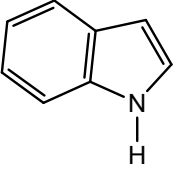
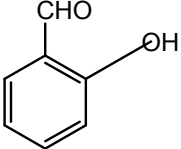
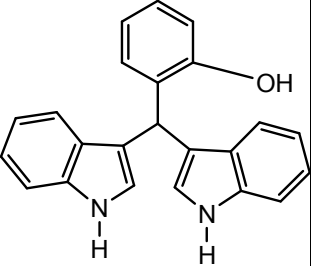
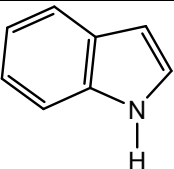
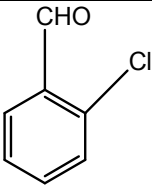
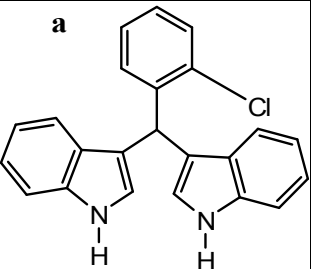
The condensation between indoles and aldehydes takes place smoothly in presence of tartaric acid catalyst. To determine the appropriate concentration of the catalyst, we investigated the model reaction at different concentrations of catalyst like 5, 10, 20, 30 and 40 mmol%. The product formed in 25, 45, 35, 65 and 82 % yield respectively. This indicates that Tartaric acid (40 mmole%) in ethanol acts as the effective catalyst by activating the carbonyl group of the aldehydes in this reaction. (Table 1, Entry 5).

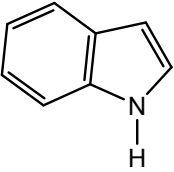
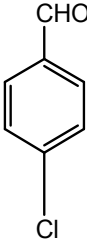
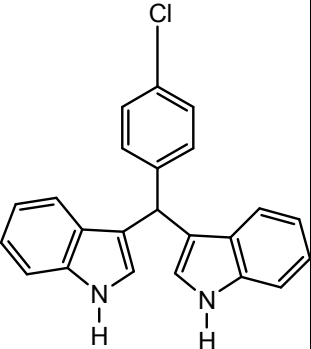
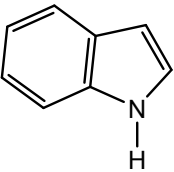
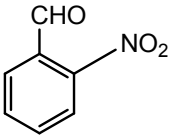
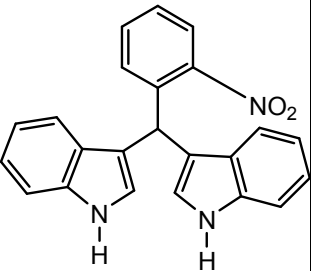
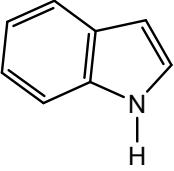
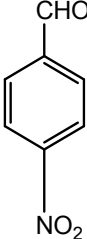
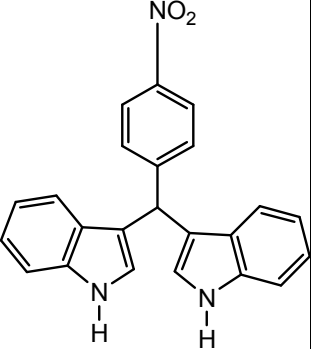
Subsequently, we studied the influence of 40 mmole% tartaric acid in ethanol as a catalyst by reaction with different substituted aromatic aldehydes with electron withdrawing as well as electron donating substituents at 60°C. Substrates with an electron-withdrawing substituent gave excellent yields in comparison with those carrying an electron-donating group, the time required was also less for electron withdrawing substituents. Both *o*-substituted and *p*-substituted aromatic aldehydes gave high yields. (Table 2)

Table-1 Effects of molar fraction of tartaric acid on the synthesis of bis(indolyl)alkanes

Entry	Mole fraction of tartaric acid (%)	Yield (%)
1	5	25
2	10	45
3	20	35
4	30	65
5	40	82

Table-2 Tartaric acid catalyzed synthesis of bis(indolyl) methanes

Entry	Indole	Aldehyde	product	Time(Hr)	Yield(%)	MP °C Obs Lit
1		CH ₃ -CHO		5	72	72
2				Nearly 4	82	86-87 (88-90)
3				4	80	177-178 (179-181)
4				3	77	120-121 (122-123)
5			a 	2.5	81	74-75 (72-74)

6				2.5	80	75-77 (76-78)
7				3	84	138-139 (140-141)
8				1	86	223 (220-224)

Experimental

All the reagents and solvents were purchased from Aldrich/Merck and used without further purification. Melting points were determined in open capillaries using Thermocal Analabapparatus and are uncorrected. The progress of the reactions as well as purity of compounds was monitored by thin layer chromatography with F254 silica-gel precoated sheets using hexane, ethyl acetate (9 :1) as eluent; UV light vapors were used for detection. IR spectra were recorded on Agilent Cary 630 FTIR Instrument, and values are expressed in cm^{-1} . ^1H NMR spectra were recorded with Bruker 400 MHz spectrometer and chemical shifts are expressed in ppm.

General Procedure for Synthesis of bis(indolyl)methanes

In a round bottom flask, indole (10 mmol) aldehyde (5 mmol), 5 ml of ethanol and catalytic amount of tartaric acid (40 mmole%) were mixed. The reaction mixture was stirred at 60°C for appropriate time (Table-2). The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured in ice cold water, obtained

product was washed thoroughly with cold water Recrystallized with ethanol to afford pure product

2) 3-((1H-indol-3-yl)(phenyl)methyl)-1H-indole: IR (Cm^{-1}) 3406.8,3050, 1416.4,1489.1, 1100, 1025, 710 $^1\text{HNMR}$ (400MHz, DMSO) : δ 5.80(S, 1H,Ar-CH), 10.73 (brS, 2H, NH),7.35-7.32 (m,4H),7.28 7.22 (m,5H), 7.03-6.99 (m,2H),6.86-6.82(m,2H),6.7(d,2H),

3)3-((1H-indol-3-yl)(4-methoxyphenyl)methyl)-1H-indole : IR (Cm^{-1})3390,2825,1505.8, 1612.1,1176,1243.1,1008.2,1092.1,800 $^1\text{HNMR}$ (400MHz,DMSO) : δ 5.77(S, 1H, Ar-CH),10.74(br S, 2H, NH), 7.35 (d,2H),7.28 (t,4H),7.05-7.009 (m,2H),6.87-6.80 (m,4H),6.77 (d,2H),3.7 (s,3H),

4) 2-(di(1H-indol-3-yl)methyl)phenol :IR (Cm^{-1}) 3401.2,3050,1416.4, 455.5,1584.1,1092.1, 1220.7, 740 $^1\text{HNMR}$ (400MHz, DMSO) : δ 6.1(S, 1H Ar-CH), 10.64(br S, 2H NH), 9.28(S, 1H),7.33-7.27(m,4H),7.07-6.95(m,4H),6.71(d,2H),6.86-6.65(m,4H),

8)3-((1H-indol-3-yl)(4-nitrophenyl)methyl)-1H-indole: IR (Cm^{-1})3390,3457, 2847.7,2920.4,1696.3,1550.8,1002.1,1220.7, 800,820 $^1\text{HNMR}$ (400MHz, DMSO) : δ 5.99 (S,1H Ar-CH) ,10.86 (br S 2H NH) ,8.13 (d, 2H), 7.59 (d,2H), 7.36(d,2H), 7.27(d,2H), 7.05 (t,2H), 6.88-6.84 (m,4H)

Conclusion

We have demonstrated an efficient way to synthesize bis-(indolyl) methane derivatives using easily available tartaric acid in ethanol as a catalyst. The procedure offers significant advantages, including mild reaction conditions, simple experimental and isolation procedures, and excellent yield of the products

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