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Environmental friendly synthesis of bis(indolyl)methanes catalyzed by nitro phthalic acids

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ABSTRACT

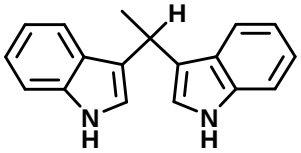
A general, mild and efficient synthesis of bis(indolyl)methanes via electrophilic substitution reaction of indole with various aldehydes or ketones under catalysis of nitrophthalic acids as potential green catalyst have been described in good yield.

KEYWORDS

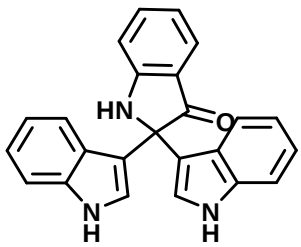
Aldehydes;
Phthalic acids;
Ketones;
Bis(indolyl)methanes;
Isatin;
EtOH.

INTRODUCTION

Bis(indolyl)alkanes and their derivatives are more attractive compounds as the bioactive metabolites of terrestrial and marine origin[1]. This unit has found to exhibit important biological activity. Vibrindole A **(1)** was demonstrated for the first time to exhibit antibacterial activity against *Staphylococcus aureus, S.albus* and *B. subtilis*[2]. Recently 2,2-Di(3-indolyl)-3-indolone **(2)** was isolated from the toxic mucus of the boxfish *ostracion cubicus* and reported to active against *Staphyloccous* aureus[3].



(1)



(2)

Consequently, numerous methods have been reported for the preparation of bis(indolyl) methanes[4]. Of these methods, the acid-catalyzed condensation of indoles with carbonyl compounds is one of most simple and straightforward approaches for the synthesis of bis(indolyl)methanes. The acids utilized in this type of reaction are protic acids such as CH_3COOH[5], HCl[6], sulphamic acid[7], $H_3PMo_{12}O_{40}$. x H_2O[8] and lewis acids sush as $InCl_3$[9], $ZrCl_4$[10], InF_3[11], $FeCl_3$[12], $In(OTf)_3$[13], $CuBr_2$[14]. Generally, these lewis acid catalysts are moisture sensitive and are easily decomposed or deactivated in the presence of the small amount of water and are thus difficult to handle, further disposal of these acids leads to environmental effluence.

At present, with the rapid development in the field of catalytic and synthetic chemistry, researchers have started to pay more attention to develop some eco-friendly catalyst, to avoid or minimize above said harmful effects. Particularly, the condensation of indoles and carbonyl compounds has been carried out success-

fully using $KHSO_4$[15], I_2[16], NBS[17], $LiClO_4$[18], CAN[19] etc. Similarly few environmentally friendly catalysts such as ion exchange resin[20], montmorillonite K-10 clay[21] and rare earth catalysts[22], zeolites[23], $NaHSO_4.SiO_2$[24], ionic liquid[25] were also appeared in literature.

Encouraged by the above survey, in the present study we investigated the catalytic activity of various phthalic acids in the synthesis of bis(indolyl)methanes formed by the condensation reaction of indole with various aldehydes and ketones. Nevertheless we have all ready explored the possibility of use of nitro phthalic acid as catalyst in the Imino Diels alder reaction[26]. Thus Phthalic acid, isophthalic acid, terephthalic acid and their nitro derivatives have found to catalyze the reaction in the synthesis of various bis (indolyl)methanes. This is the first report for the use of these acids as catalysts in bis (indolyl)methane synthesis.

EXPERIMENTAL

All the melting points were recorded in open capillary and were compared with the literature.[5,15] The purity of the compounds was checked by TLC on silica gel and were purified by column chromatography. ^{1}H NMR spectra were recorded on a Bruker-300

MHz spectrometer with DMSO as the solvent and TMS as an internal standard. IR spectra were obtained using a FTS-135 spectrometer instrument. Mass spectras were recorded on a JEOL SX 102/DA-6000 (10kV) FAB mass spectrometer. Solvents, Chemicals and reagents were purchased from Merck chemical company in high-grade quality.

General procedure

4-nitro phthalic acid (1.0 mmol) was added to a mixture of indole (2.0 mmol) and aldehydes or ketones (1.0 mmol) in ethanol (10 mL). The reaction mixture was stirred at room temperature for the appropriate time (TABLE 3). After the completion of the reaction, it was quenched with water (10mL) and extracted with ethyl acetate (2 X 15 mL). And combined organic layer were dried over anhydrous sodium sulphate, concentrated and the crude product was purified by silica gel column chromatography and eluted with an ethyl acetate and petroleum ether mixture to afford bis(indolyl)methane.

3, 3'-bis-indolyl (phenyl) methane (3a)

Pink solid; mp 124–125 ^{o}C; IR (KBr) 3415, 3025, 1631, 1380, 1265, 1008, 734 cm^{-1}; ^{1}H NMR ($CDC1_3$) d ppm: 7.89 (brs, 2H, NH), 7.38 (d, *J*=7.8 Hz, 2H), 7.33–7.35 (m, 4H), 7.19–7.30 (m, 5H), 7.00 (m, 2H), 6.64 (d, *J*=1.1 Hz, 2H), 5.88 (s, 1H); MS: m/z 322 (M^+).

4-Methoxyphenyl-3, 3'-bis(indolyl)methane (3b)

Pinkish solid; mp 192-193 ^{o}C; IR (KBr): 3392, 3055, 2933, 2838, 1610, 1507, 1320, 1023, 743 cm^{-1}; ^{1}H NMR ($CDCl_3$): ^{1}H NMR ($CDCl_3$): d ppm: 7.93 (brs, 2H, NH), 7.26–7.38 (m, 8H), 7.18 (t, *J*=7.8 Hz, 2H), 7.02 (t, 2H, *J*=7.6 Hz, 2H), 6.65 (s, 2H), 5.86 (s, 1H); 3.77 (s, 3H); MS: m/z 352.17 (M^+).

4-Chlorophenyl-3, 3-bis(indolyl)methane (3d)

Pink solid; mp 78-80 ^{o}C; IR (KBr): 3411, 3055, 2923, 2848, 1617, 1417, 1327, 1013, 743 cm^{-1}; ^{1}H NMR ($CDCl_3$) d ppm: 7.93 (brs, 2H, NH), 7.26–7.38 (m, 8H), 7.18 (t, *J*=7.8 Hz, 2H), 7.02 (t, 2H, *J*=7.6 Hz, 2H), 6.65 (s, 2H), 5.86 (s, 1H); MS: m/z 356 (M^+).

1-(di-1*H*-indol-3-ylmethyl)-2-naphthol (3i)

Yellow solid; mp 203-205 ^{0}C; IR (KBr): 3415, 3020,1605, 1460, 1290, 1068, 1004, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) d ppm: 12.2 (s, 1H), 8.15 (d, *J*=8.6 Hz, 1H), 8.06 (brs, 2H, NH), 7.83 (d, *J*=8.0 Hz, 1H), 7.73 (d, *J*=8.0 Hz, 1H), 7.3-7.45 (m, 7 H), 7.2 (t, *J*=7.2 Hz, 2H), 7.02 (t, *J*=7.6 Hz, 2H), 6.82 (s, 1H), 6.76 (s, 1H), 6.5 (s, 1H, CH); MS: m/z 388 (M^+).

3,3'-(2,3-dihydro-1,4-benzodioxin-6-ylmethanediyl) bis (1*H*-indole) (3q)

Pink red: mp 238-240 ^{0}C ; ^{1}H NMR (DMSO d_6) d ppm: 10.76 (br, NH,2H), 7.3 (m, 2H), 7.03 (t, *J*=7.08 Hz, 2H), 6.8 (d,*J*= 7.07 Hz, 2H), 6.7 (m, 6H), 5.6 (s, 1H), 4.1 (s, 4H). ^{13}C NMR: 143.4,141.1, 136.4, 132.6, 139.9, 121.7, 120.5, 119.6, 115.5, 113.7, 112.1, 111.0, 75.2, 44.2. MS: m/z 379.2 (M-1).

1*H*,1''*H*-3,3':3',3''-terindol-2'(1'*H*)-one (3r)

Brown Solid: mp 248-250 ^{o}C; ^{1}H NMR (DMSO d_6) d ppm: 10.92 (brs, s 2H), 10.56 (s,1H),7.34 (d, *J*=8.01 Hz, 2H), 7.23 (t, *J*=6.3 Hz, 4H), 6.99 (m, 4H), 6.8 (m, 4H): ^{13}C (75, MHz, $CDCl_3$) 196.5, 143.2,

135.5, 133.7, 132.1, 130.5, 122.2, 121.7, 121.2, 120.5, 119.6, 116.8, 112.2, 112.1, 111.0, 86.5. MS: m/z 362.4 (M-1).

5'-bromo-1*H*,1''*H*-3,3':3',3''-terindol-2'(1'*H*)-one(3s)

Yellow Solid: mp 248-250 °C; ^{1}H NMR (DMSO d_6) d ppm: 10.99 (brs, 2 NH), 10.72 (s, NH), 7.36 (d, *J*=8.07 Hz, 2H), 7.26 (d, *J*=19.53 Hz, 3H), 7.16 (d, *J*=2.37 Hz, 3H), 7.03 (m, 5H) 6.87 (d, *J*=3.6 Hz, 2H), 6.82 (d, *J*=7.89 Hz, 2H). ^{13}C (75, MHz, $CDCl_3$) 194.5, 141.5, 136.8, 136.2, 132.8, 131.6, 122.8, 122.1, 121.5, 120.5, 119.6, 112.1, 111.2, 111.0, 86.2. MS: m/z 440 (M-2).

5'-chloro-1*H*,1''*H*-3,3':3',3''-terindol-2'(1'*H*)-one (3t)

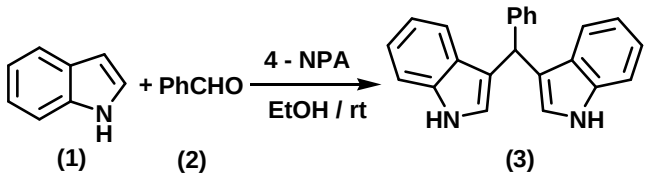
White Solid: mp 260-262 °C; ^{1}H NMR (DMSO d_6) d ppm:10.99 (s, 2H, NH), 10.72 (s, 1H, NH), 7.36 (d, *J* = 8.07 Hz, 2H), 7.26 (d, 1H), 7.19 (d, *J* = 8.55 Hz, 3H). 7.03 (m, 3H), 6.87 (d, *J*=2.4 Hz, 2H), 6.80 (d, *J*=7.89 Hz, 2H).^{13}C (75, MHz, $CDCl_3$) 196.2, 141.2, 136.5, 134.1, 131.2, 129.7, 122.2, 121.9, 120.9, 120.5, 119.6, 113.6, 112.1, 111.0, 86.1, MS: m/z 396.2 (M-1).

5'-fluoro-1*H*,1''*H*-3,3':3',3''-terindol-2'(1'*H*)-one (3u)

Brown Solid: mp 245-247 °C; 1H NMR (DMSO d_6) d ppm: 10.97 (brs, s, 2H), 10.60 (s, 1H), 7.35 (d, *J*=8.1 Hz, 2H), 7.21 (d, *J*= 8.34 Hz, 2H), 7.05 (m, 4H), 6.87 (d, *J*=2.55 Hz, 2H), 6.82 (t, *J*=7.23 Hz, 2H). ^{13}C (75, MHz, $CDCl_3$) 196.5, 142.6, 134.2, 133.5, 132.7, 130.6, 123.4, 122.1, 121.7, 120.5, 119.6, 112.2, 111.4, 111.0, 86.1. MS: m/z 380.1 (M-1).

RESULTS AND DISCUSSION

Initially, we examined the 4-Nitro Phthalic acid (4-NPA) in the model reaction of indole with benzaldehyde (Scheme 1) in different reaction media to investigate the solvent effect. The results are summarized in TABLE 1 and shows that polar solvents are much better than nonpolar solvents. Remarkably, the condensation proceeded smoothly in acetonitrile and to afford desired product in good yield (85%). However, the ethanol was found to be best for the catalytic reaction at room temperature in terms of yield, reaction time and product isolation.



Scheme 1

The catalytic activities of different nitro derivatives of phthalic acids were also tested and the results are shown in TABLE 2. Interestingly, the reaction time as well as the yield differs for each derivative. 4-nitro phthalic acid (4-NPA) is found to be a good catalyst compared to other phthalic acids. The minimum activity concentration of 4-nitrophthalic acid was also tested. It was observed that, the yield depended on the amount of the catalyst loading, and in the presence of 25mol% (based on the amount of indole) of 4-nitro phthalic acid, the reaction afforded 95% yield of the corresponding bis(indolyl) methanes in 3h in case of benzaldehyde. Further studies show that increasing the amount of catalyst did not give better yield but reduced the reaction time (entry 9 in TABLE 2).

TABLE 1 : Effect of solvents in the reaction of indole with benzaldehyde catalyzed by 4-nitro phthalic acid at room temperature.

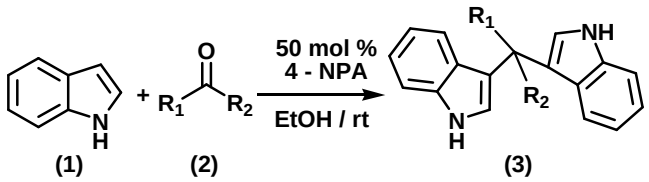
Solvents	Yield (%)[a]
EtOH	95
MeOH	94
CH_3CN	85
$C_2H_5OC_2H_5$	80
Toluene	30
Benzene	20

[a]**Isolated yields**

Using these optimized conditions, we examined the reaction of various aldehydes and ketones with indole in the presence of 4-NPA to afford bis(indolyl)methanes (Scheme 2).

The results are summarized in TABLE 3. In all cases, the electrophilic substitution reaction of indoles with aldehydes could proceed smoothly at room temperature to produce the corresponding bis(indolyl)methanes in good yield in shorter times. Whereas the reaction of the

ketones and indole took longer time when compared with aldehydes, and unreacted ketones and indole remained the same.

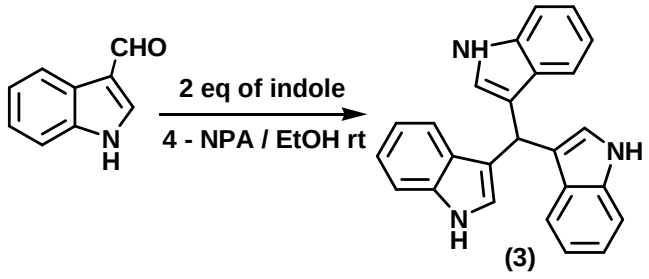


R_1 = aliphatic or aromatic substitutes

R_2 = H, CH_3

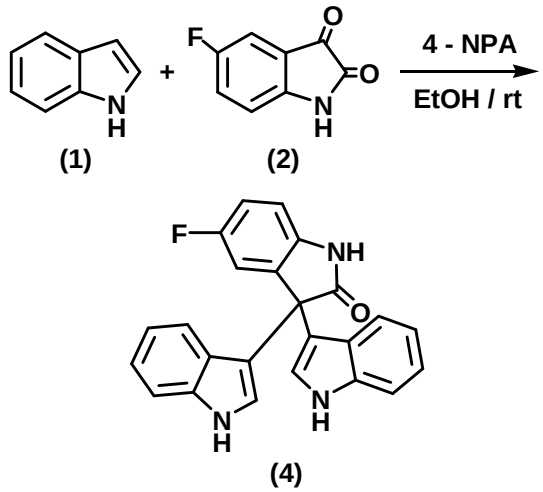
Scheme 2

Further, we also tried to explore the catalytic activities of 4-NPA, to seek the general, mild and efficient of this method of accessing the bisindolylalkane framework. We then sought to apply the methodology to preparing a variety of naturally-occurring compounds. We first targeted vibrindole A **(1)**, which was obtained in 80% yield from the reaction of acetaldehyde and indole. Then trisindolylalkane **(3)** (Scheme 3) isolated from the bacterium *Vibrio parahaemolyticus*[27], was prepared by the reaction of indole-3- carboxaldehyde and indole in 75% yield. We were also able to obtain the compound **(4)** (Scheme 4), from the coupling of isatine and two equivalents of indoles, which is structurally very close to 2,2-Di(3-indolyl)-3-indolone **(2)** was isolated from the toxic mucus of the boxfish *ostracion cubicus*.



Scheme 3

Thus 5-Fluroisatin (0.1gm 0.60 mmol) underwent smooth condensation with indole (0.141gm 1.20 mmol) to produce 6-fluoro-1,1-di-1*H*-indol-3-yl-1,3-dihydro-2*H*-inden-2-one with good yields without the need for column chromatography. This clearly shows that 4-NPA is not only suitable to activate indoles and simple aldehydes, but it is also suitable to activate stearically congested keto group of isatin.



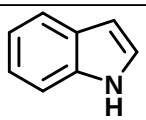
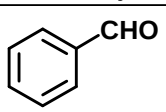
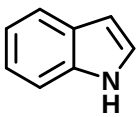
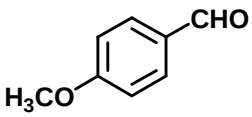
Scheme 4

TABLE 2 : Effect of catalysts in the reaction of indole with benzaldehyde in EtOH at room temperature

Entry	Catalyst	Time (h)	Yield(%)[a]
1	phthalic acid	8	78
2	4-nitro phthalic acid	3	95
3	3-nitro phthalic acid	8	85
4	3,5-dinitro phthalic acid	6	86
5	Isophthalic acid	10	55
6	5-nitro Iso-P.hthalic acid	12	68
7	Terephthalic acid	48	38
8	2-nitro tere. p acid	38	52
9	4-Nitrophthalic acid [b]	2	95

[a]Isolated yields; [b]50 mol% of catalyst.

TABLE 3 : Scope of bisindolylalkane formation catalyzed by 4-NPA[a]

Product	Indole	Carbonyl	Time (h/min)	Yield (%)[b]
3a			3.00	95
3b			1.30	96

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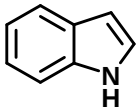
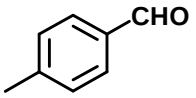
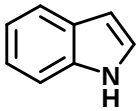
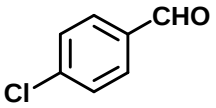
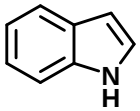
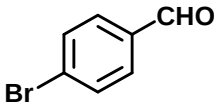
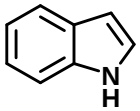
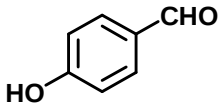
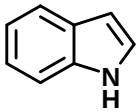
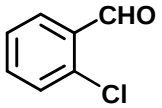
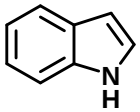
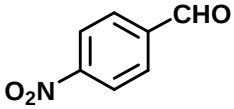
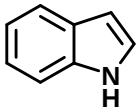
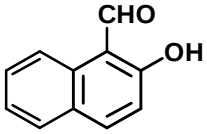
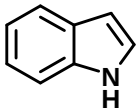
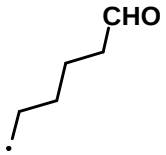
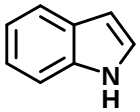
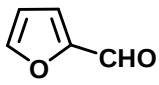
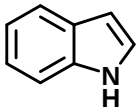
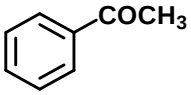
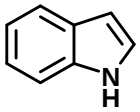
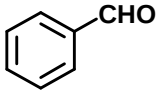
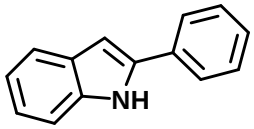
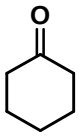
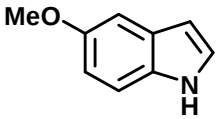
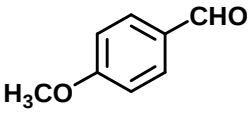
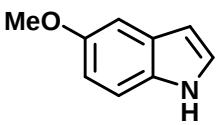
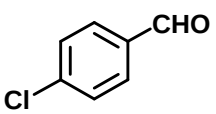
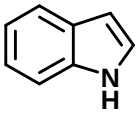
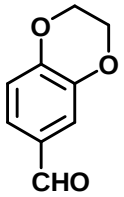
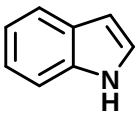
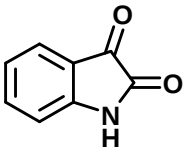
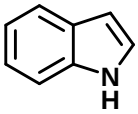
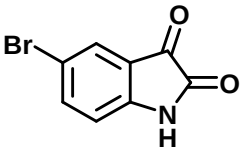
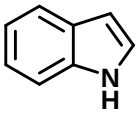
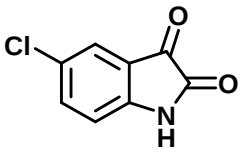
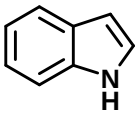
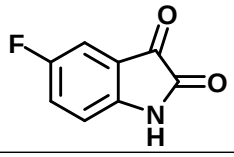
Product	Indole	Carbonyl	Time (h/min)	Yield (%)[b]
3c			1.45	95
3d			2.30	90
3e			2.30	92
3f			3.30	88
3g			1.15	94
3h			4.00	90
3i			3.30	86
3j			4.00	85
3k			3.45	88
3l			24.00	48
3m			2.00	96
3n			16.00	78
3o			2.30	90
3p			2.30	84

Product	Indole	Carbonyl	Time (h/min)	Yield (%)[b]
3q			2.00	90
3r			1.30	94
3s			0.45	95
3t			4.00	90
3u			4.30	92

[a]The reaction was carried out in EtOH at r. t. [b]Isolated yields.

CONCLUSION

We have investigated the catalytic properties of novel phthalic acid, isophthalic acid, terephthalic acid and its nitro derivatives in the condensation of indoles with aldehydes and ketones. 4-nitro phthalic acid served as mild and effective catalyst for the condensation of the indole with aldehydes and ketones in EtOH at room temperature in the presence of both moisture and air, to afford bis(indolyl)methanes in high yields compared to other acid derivatives. This method offers several significant advantages such as high conversions; easy handling, cheaper catalyst, cleaner reaction profiles, short reaction time and the reaction conditions are amenable to scaling since the catalysts used are environmentally friendly.

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