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p-Toluenesulfonic Acid (*p*-TSA) Catalyzed Efficient Synthesis of bis(indolyl)methanes under *Grindstone* Method

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Abstract: An efficient reaction of indole with various aldehydes and ketones using catalytic amount of *p*-TSA to afford the corresponding bis (indolyl) methanes under *Grindstone* method in the absence of solvent is reported. The products are obtained in excellent yields.

Key words: Bis(indolyl) methanes, indole, aldehydes, *p*-TSA, *Grindstone* method

Introduction

Indole fragment is featured widely in a variety of pharmacologically and biologically active molecules including those having antibacterial, antibiotic, cytotoxic, antioxidative and insecticidal activities (Sundberg., 1970). Bis (indolyl) methanes isolated from marine sources (Bell *et al*., 1994) have become interesting targets to synthetic organic chemists and biologists. Among the many methods, the synthesis of this class of compounds involves reaction of indole and an aromatic or aliphatic aldehyde or a ketone and a suitable Lewis acid or Brönsted acid catalyst. The reported methods include use of $InCl_3$ or $In(OTf)_3$ (Nagarajan and Perumal, 2002), $Ln(OTf)_3$ (Chen *et al*., 1996), $LiClO_4$ (Yadav *et al*., 2001), VCl_3 (Rajitha *et al*., 2005), $CuBr_2$ (Mo *et al*., 2005), trichloro-1,3,5-triazine (Sharma *et al*., 2004), Zeolite (Karthik *et al*., 2004; Reddy *et al*., 2003) and molecular iodine (Ji *et al*., 2004; Bandagar *et al*., 2003), use of sulphamic acid (Singh *et al*., 2005), polyindole salt (Palaniappan and John, 2005), Montmorillonite clay K-10 (Ramesh *et al*., 2003), rare earth perfluorooctanoate $[RE(PFO)_3]$ (Wang *et al*., 2005) and ionic liquid (Gu *et al*., 2005). Other methodologies like microwave/silica chloride (Das *et al*., 2005) and ultrasound/CAN (Zeng *et al*., 2005; Ramesh *et al*., 2003) are also documented in the literature. However, the yields of some examples are not satisfactory and the mentioned methods usually involve expensive reagents and relatively harsh conditions are employed for the reaction and longer time durations are required for completion. Some other methods involve tedious experimental procedures and complex reaction mixtures are obtained and thus the yields are low and some of the acid catalysts may decompose the indoles and affect the functionalities.

Toda *et al*. (1987) and Bose *et al*. (2004) have introduced a novel method called Grindstone method. In *Grindstone* method the reactants are ground together to get the products. The method is advantageous over the existing methods as the yields of the products are high and one can avoid the use of solvents for the reaction.

Materials and Methods

Melting points were determined on a Buchi melting point apparatus. IR, ^1H NMR GC-MS spectra were recorded on Nicolet 400D FT-IR spectrophotometer, 400 MHZ Brucker spectrometer and Shimadzu GC-MS QP 5050A respectively. Indole, aldehydes/ketones and *p*-TSA were all commercial products and used without further purification.

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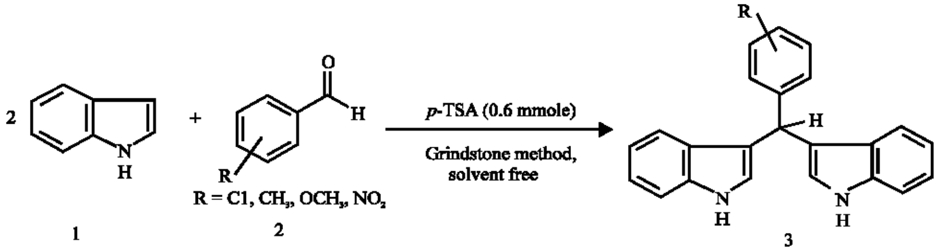
General Procedure for the Synthesis of 1H,1' H-3,3'-(4-Nitro-Phenylmethanediyl)-bis-indole

A mixture of *p*-nitrobenzaldehyde (1.51 g, 10 mmole), indole (2.34 g, 20 mmole) and *p*-TSA (0.12 g, 0.6 mmole) were ground together with a pestle and mortar at 25°C, the syrupy reaction mixture solidified, the contents were quenched by adding water and EtOAc. The organic layer was used to check the disappearance of the starting material by TLC. After completion (8 min), the solid was washed with water and extracted by ethyl acetate (2×25 mL). The organic layer was dried over anhydrous sodium sulphate, concentrated in vacuo and purified by column chromatography (EtOAc: Petroleum ether = 1:9) to afford the pure 1*H*,1'*H*-3,3'-(4-Nitro-phenylmethanediyl)-bis-indole (3d, 3.37 g, 92%)

Results and Discussion

We have recently reported the synthesis of 1,5-benzodiazepine derivatives from o-phenylene diamine and ketones in the presence of catalytic *p*-TSA (Pasha and Jayashanakra, 2006). In continuation of work on the use of *p*-TSA, we have been able to use *p*-TSA as a catalyst for the synthesis of bis (indolyl) methanes under *Grindstone* method and in this study we are reporting the synthesis of bis (indolyl) methanes from two equivalent of indole and one equivalent of an aldehyde or a ketone in the presence of *p*-TSA by grinding all the three for about 3–8 min (Scheme 1).



Scheme 1.

When compared to the other reported methods, we have found that *p*-TSA in solvent-free condition is found to be an efficient catalyst for the synthesis of bis (indolyl) methanes under Grindstone method. The reaction of indole with aldehydes and ketones proceeds smoothly at room temperature to afford the corresponding bis (indolyl) derivatives in high yields in a short reaction time. Results summarized in Table 1, clearly indicate the scope of the reaction with respect to various substituted aldehydes and ketones. Comparison of existing catalysts and different methodologies used to prepare bis (indolyl) methanes with that of the present method is presented in Table 2.

Spectral Data for All the Prepared Products

1H,1'H-3,3'-Phenylmethanediyl-bis-indole (3a)

IR (KBr): ν 742, 1088, 398, 1603, 1621, 3098, 3425 cm^{-1}

^{1}H NMR (400 MHZ, CDCl$_3$): δ = 5.85 (s, 1H, Ar-CH), 6.72 (s, 2H), 7.02 (t, 2H, J = 6.7Hz), 7.12-7.20 (m, 3H), 7.25-7.30 (m, 2H), 7.34-7.40 (m, 6H), 7.90 (br, 2H, NH).

MS: m/z = 322 (M$^+$).

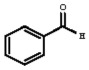
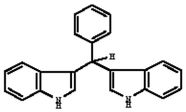
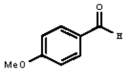
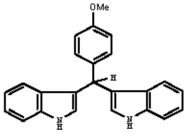
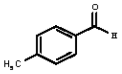
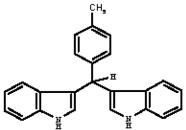
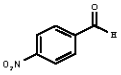
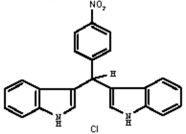
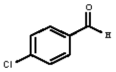
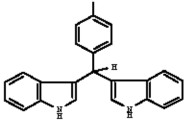
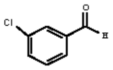
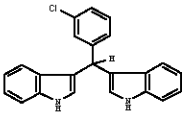
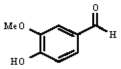
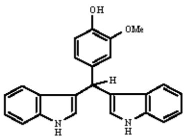
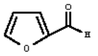
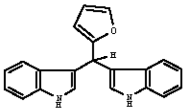
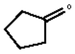
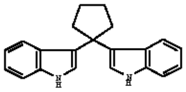
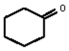
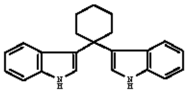
1H,1'H-3,3'-(4-Methoxy-Phenylmethanediyl)-bis-indole (3b)

IR (KBr): ν 1223, 1230, 1462, 1520, 1613, 2942, 3418 cm^{-1}

^{1}H NMR (400 MHZ, CDCl$_3$): δ = 3.75 (s, 3H, CH$_3$), 5.78 (s, 1H, Ar-CH), 6.62 (s, 2H), 6.80 (d, 2H, J = 8.2 Hz), 7.16 (t, 2H, J = 7.2Hz), 7.16 (t, 2H, J = 7.3Hz), 7.21 (s, 2H), 7.26-7.40 (m, 4H), 7.87(br, 2H, NH).

MS: m/z = 380 (M$^+$).

Table 1: *p*-TSA catalysed synthesis of bis (indolyl) methanes

Entry	Aldehyde /ketone (2)	Product[a] (3)	Time (min)	Yield[b] (%)	Melting point (°C) Found	Melting point (°C) Reported[c]
a			5	83	152	150-52
b			3	90	187-88	187-89
c			6	87	94-5	94-6
d			8	92	217-18	219
e			5	95	77	76-77
f			5	93	73	74
g			5	70	110	110-12
h			4	90	112-13	113-15
I			8	87	73-4	72-4
j			8	85	119-20	118-20

[a] All the products are known, characterized by IR, 1H NMR and MS spectral analysis and compared with the authentic samples. [b] Isolated yields. [c] Melting points of compounds are consistent with reported values (references Singh *et al.*, 2005; Reddy *et al.*, 2003; Li *et al.*, 2005)

1H, 1'H-3,3'-(4-methyl-phenylmethanediyl)-bis-indole (3c)

IR (KBr): ν 772, 1062,1216, 1520, 1613, 2948, 3421 cm^{-1}

^{1}H NMR (400 MHZ, $CDCl_3$): δ = 2.38 (s, 3H, Ar-CH_3), 5.82 (s, 1H, Ar-CH), 6.65

Table 2: Comparison of results of reactions with different catalysts for the synthesis of bis(indolyl)methane derivatives

Catalysts	Time	Temp.°C	Yield (%)[b]
In $(OTf)_3$ (Nagarajan and Perumal, 2002)	25-30 min	25	71-86
Ln $(OTf)_3$ (Chen *et al*., 1996)	12-24 h	25	77-99
$LiClO_4$ (Yadav *et al*., 2001)	2-8 h	25	80-90
Zeolite HY (Karthik *et al*., 2004)	1-1.5 h	25	72-85
$CuBr_2$ (Mo *et al*., 2005)	24 min-8 h	25	75-95
VCl_3 (Rajitha *et al*., 2005)	30-45 min	25	92-95
Silica chloride (Das *et al*., 2005)	1 min	Microwave	85-95
CAN (Zeng *et al*., 2005)	2.5 h	Ultrasound	75-96
p-TSA [a] (Present method)	8 min	Grindstone	92.00

[a]Reaction condition: p-nitrobenzaldehyde (10 mmole), indole (20 mmole) and p-*TSA* {p-*toluenesulfonic acid*} (0.6 mmole) grind together afford product 3d. [b] Isolated yields

(s, 2H), 6.97 (t, 2H, J =7.5 Hz), 7.2 (d, 2H, J = 7.3Hz), 7.19-7.26 (m, 6H), 7.2 (d, 2H, J = 7.3Hz), 7.91 (br, 2H, NH).

MS: m/z = 336 (M^+).

1H, 1'H-3,3'-(4-Nitro-phenylmethanediyl)-bis-indole (3d)

IR (KBr): ν 1353, 1472, 1562, 1600, 3052, 3432 cm^{-1}

^{1}H NMR (400 MHZ, $CDCl_3$): δ = 6.18 (s, 1H, Ar-CH), 6.76 (s, 2H), 7.0-7.05 (m, 3H), 7.42 (d, 3H, J = 7.8 Hz), 7.4 (d, 2H, J = 7.9Hz), 7.49 (d, 2H, J = 8.6 Hz), 7.97 (br, 2H, NH), 8.00 (d, 2H, J = 8.3 Hz).

MS: m/z = 367 (M^+).

1H, 1'H-3,3'-(4-Chloro-phenylmethanediyl)-bis-indole (3e)

IR (KBr): ν 1092, 1474,1502, 3052, 3430 cm^{-1}

^{1}H NMR (400 MHZ, $CDCl_3$): δ = 6.02 (s, 1H, Ar-CH), 6.67 (s, 2H),7.12(t, 3H, J = 8.5 Hz), 7.20 (t, 2H, J = 7.9Hz), 7.27-7.40 (m, 8H), 7.97 (br, 2H, NH).

MS: m/z = 356 (M^+).

1H, 1'H-3,3'-(3-Chloro-phenylmethanediyl)-bis-indole (3f)

IR (KBr): ν 1067, 1484,1512, 3082, 3473 cm^{-1}

^{1}H NMR (400 MHZ, $CDCl_3$): δ = 6.12 (s, 1H, Ar-CH), 6.71 (s, 2H), 7.16 (t, 3H, J = 8.7 Hz), 7.22 (t, 2H, J = 8.0 Hz), 7.32-7.43 (m, 8H), 8.0 (br, 2H, NH).

MS: m/z = 356 (M^+).

1H, 1'H-3,3'-(4-hydroxy-5-methoxyphenylmethanediyl)-bis-indole (3g)

IR (KBr): ν 752, 1397,1652, 3422, 3498 cm^{-1}

^{1}H NMR (400 MHZ, $CDCl_3$): δ = 9.92 (br, 2H) 7.90 (s, 1H), 7.35-6.92 (m, 11H), 6.66 (s, 2H), 5.78 (s, 1H), 3.72 (s, 3H).

MS: m/z = 368 (M^+).

Diindol-3-yl-[2]oxyeny1-methane (3h)

IR (KBr): ν 1278, 1464,1732, 3428 cm^{-1}

^{1}H NMR (400 MHZ, $CDCl_3$): δ = 6.23 (s, 1H, Ar-CH) 6.93 (s, 2H), 7.35-6.78 (m, 11H),8.12 (br, 2H, NH).

MS: m/z = 312 (M^+).

1H, 1'H-3,3'-Cycopentylmethanediyl-bis-indole (3i)

IR (KBr): ν 3482, 2978,1635,1595, 1498, 1032, 778 cm^{-1}

^{1}H NMR (400 MHZ, $CDCl_3$): δ = 1.78 (m, 4H) 2.52 (m, 4H), 6.80 (t, 2H, J = 8.2 Hz),7.02 (m, 4H), 7.23 (d, 2H, J = 8.2Hz), 7.50(d, 2H, J = 8.2 Hz) 7.92(br, 2H, NH).

MS: m/z = 300 (M^+).

1H, 1'H-3,3'-Cyclohexylmethanediyl-bis-indole (3j)

IR (KBr): ν 3472, 3035,2986,1635, 1592, 1492, 1239, 1019, 785 cm^{-1}

^{1}H NMR (400 MHZ, $CDCl_3$): δ = 1.82 (m, 6H) 2.57 (m, 4H), 6.83 (t, 2H, J = 8.2 Hz), 7.07 (m, 4H), 7.27 (d, 2H, J = 8.2Hz), 7.53 (d, 2H, J = 8.2 Hz) 7.90 (br, 2H, NH).

MS: m/z = 314 (M^+).

Conclusions

In conclusion, we have demonstrated an efficient reaction of indole with various aldehydes and ketones using catalytic amount of *p*-TSA to afford the corresponding bis (indolyl) methanes under Grindstone method in the absence of solvent, this procedure is much simpler and faster than other exciting methods. It is also consistent with the green chemistry approach, the catalyst used is an inexpensive chemical that is commonly found in most organic chemistry laboratories.

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