Synthesis of Bis 1*h*-Indole Methane Derivatives Using Cellulose Perchloric Acid Under Solvent-Free Conditions

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Abstract

Indoles and their derivatives are used as antibiotics in the field of pharmaceuticals Bis(indolyl)alkanes and their derivatives constitute an important group of bioactive metabolites. Cellulose Supported Perchloric Acid (CSPA) was found to be a mild, efficient and reusable solid acid catalyst in electrophilic substitution reaction of indoles with various aldehydes and ketones to afford the corresponding bis(indolyl)methane. The significant features of this method are excellent yields of the products under solvent-free conditions and non-toxicity of the catalyst.

KEYWORDS: CSPA, bis(indolyl)methane, carbonyl compounds and indole.

Introduction

Indoles and their derivatives have emerged as important class of nitrogen heterocycles attracting significant synthetic interest because of their pharmaceuticals and agrochemicals properties. synthesis of bis(indolyl)alkane has been develop considerable interest in organic synthesis because of their wide occurrence in various natural products possessing biological activity[1] and usefulness for drug design.[2] Indoles and their derivatives are used as antibiotics in the field of pharmaceuticals[3] . It was affect the central nervous system and so are used as tranquilizers. It's effect in the prevention of cancer due to its ability to modulate certain cancer causing estrogen metabolites[4]. Bis(indolyl)alkane and their derivatives constitute an important group of bioactive metabolites of terrestrial. Substituted indole units in a molecule feature widely in Pharmacology, medicinal and biochemistry[5]. These compounds can be prepared from the reaction of indoles with various aldehydes and ketones. A great number of methods have been reported in the literature for the preparation of bis(indolyl)methane in which protic acids,[6] as well as Lewis and other acids, such as $LiClO_4$[7], Lewis acid catalysts such as I_2[8], hexamethylenetetramine–bromine[9], $ZrOCl_2$[10], p-toluene sulfonic acid[11], $[bnmim][HSO_4]$[12], NH_4Cl[13], $AlPW_{12}O_40$ [14], TPA-ZrO_2 [15], $Zr(DS)_4$ [16], sulfamic acid [17], $ZrCl_4$[18], trichloro-1,3,5-triazine[19] and $ZrOCl_2$ $8H_2O$–silica gel[20]. Several catalyst including lanthanide triflate[21] $Dy(OTf)_3$[22], $InCl_3$[23], PPh_3-$HClO_4$[24], montmorilonite K-10[25], NBS[26], $KHSO_4$[27], $RE(PFO)_3$[28], InF_3[29], and acidic ionic liquid[30] were found to promote the reaction.

One of the ultimate goals for organic reactions is to reduce the use of harmful organic solvents. For this reason, over the last few years enormous advances have been made to achieve the environment friendly chemical processes. One way for this purpose is carrying out the reactions in solvent-free conditions[31]. Recently, Shingare and co-workers reported synthesis of few derivatives of bis(indolyl)methanes using cellulose sulfuric acid[32]. In the present article, we report a facile route using

Cellulose Supported Perchloric Acid (CSPA) as an efficient catalyst for the synthesis of widespread range of bis(indolyl)methanes derivatives. It is non-explosive, easy handling, eco-friendly, stable and recoverable solid acid catalyst.

Material And Methods

***Synthesis of indole derivatives*:**

To the mixture of indole (2.0 mmol), an aromatic aldehyde (Table-01) (1.0 mmol) and Cellulose Supported Perchloric Acid (0.1 g, 5 mol. %) was added and the mixture was ground at room temperature until the disappearance of the starting materials. After completion of the reaction as indicated by TLC, Ethanol was added to the reaction mixture and then filtered. The filtrate was evaporated under reduced pressure to afford crude product which was then purified by column chromatography and eluted with ethyl acetate and petroleum ether mixture (1:9) to afford the pure product (Table-02). The products were identified by melting point, IR and 1H NMR data.

Scheme

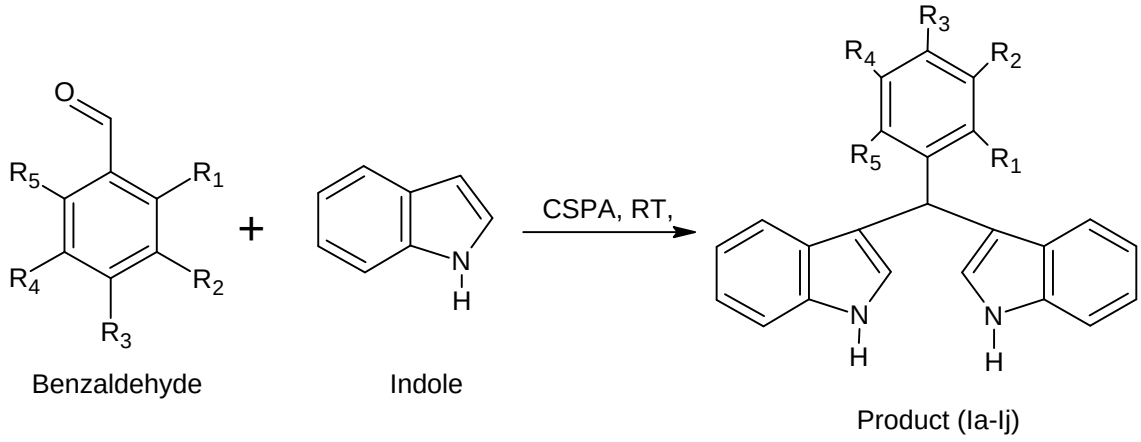

Table 1 Different substituent of aromatic aldehydes.

Compounds	R_1	R_2	R_3	R_4	R_5
Ia	H	H	H	H	H
Ib	Cl	H	H	H	H
Ic	H	H	Cl	H	H
Id	H	H	OCH_3	H	H
Ie	H	OCH_3	OCH_3	H	H
If	H	OCH_3	OH	H	H
Ig	H	H	NO_2	H	H
Ih	H	NO_2	H	H	H
Ii	H	H	$N(CH_3)_2$	H	H
Ij	H	H	CH_3	H	H

Table 2 Yield and time required for synthesis of bis(indolyl)methane derivatives.

Sr.	Entries	Time (min)	Yield	Melting Point Found	Melting Point Reported
1	Ia	32	90%	126^0C	(125-127^0C)
2	Ib	40	87%	71^0C	(72-74^0C)
3	Ic	14	90%	79^0C	(77-81^0C)
4	Id	40	83%	189^0C	(187-189^0C)
5	Ie	23	92%	110^0C	(110-112^0C)
6	If	25	80%	196^0C	(198-200^0C)
7	Ig	15	88%	221^0C	(220-222^0C)
8	Ih	24	90%	263^0C	(263-268^0C)
9	Ii	32	94%	121^0C	(120-127^0C)
10	Ij	10	89	97^0C	(95-97^0C)

Results and Discussion

Initially the reaction of benzaldehyde (1mmol) with indole (2mmol) for the synthesis of Bis(indolyl)Methane form, and examined the required time, temperature and the molar ratio of catalyst. We observed that Cellulose Supported Perchloric Acid (CSPA) is an effective catalyst for this reaction in terms of the amount of catalyst and reaction time in compare with recently reported solid acid. Very small amount of CSPA was required to give the most satisfactory yield within short period of time at room temperature under solvent-free condition. It is important that after completion of the reaction, the catalyst can be separated by simple filtration and recovered cellulose perchloric acid can be reused in subsequent reactions without significant decrease in activity. It is clear that we have developed an economically and environmentally beneficial procedure for the preparation of Bis(indolyl)Methane in presence of cellulose supported perchloric acid catalyst. This catalyst is bio-supported and recyclable solid acid catalyst. By using this catalyst we can perform eco-friendly chemistry with operational simplicity and high yield.

Spectroscopic Data

Ia (3, 3'-Bis (indolyl) phenylmethane)

IR (KBr): 3402, 3051, 1618, 1600 1017, 757, 669 cm^{-1}.

^{1}H--NMR ($CDCl_3$,): δH 5.82 (s, 1H, C–H), 6.62(s, 2H, C–H), 7.14(t, 2H, Ar-H, *J* = 6.9 Hz), 7.16–7.28 (m, 3H, Ar-H), 7.26–7.36 (m, 2H, Ar-H), 7.35–7.42 (m, 6H, Ar-H), 7.94 (br, 2H, NH).

Ic (3, 3'-Bis (indolyl)-4-chlorophenylmethane)

IR (KBr): 3474, 3024, 2920, 1606, 1523, 1456, 1091, 1015, 759 cm^{-1};

^{1}HNMR ($CDCl_3$): δH 5.82 (s, 1H), 6.64 (bs, H), 7.02-7.74(m, 12H), 7.96(bs, 2H NH).

Id (3, 3'-Bis (indolyl)-4-methoxyphenylmethane)

IR (KBr): 3476, 3022, 2808, 1610, 1509, 1455, 1091, 1033, 759 cm^{-1};

^{1}HNMR ($CDCl_3$): δH 3.72(s, 3H,), 5.88(s, 1H), 6.68(d, 2H), 6.82(d, 2H), 7.06(t, 2H), 7.4(t, 2H); 7.24-7.42(m, 6H), 7. 29(bs, 2H NH).

Ie (3, 3'-Bis (indolyl)-3, 4-dimethoxyphenylmethane)

IR (KBr): 3480, 3020, 1604, 1512, 1456, 1418, 1033, 759 cm^{-1};

^{1}H NMR ($CDCl_3$): δH 3.78(s, 3H), 3.88(s, 3H), 5.82(s, 1H), 6.68(d, 2H), 6.82(d, 2H), 7.1(t, 3H), 7.19(t, 2H), 7.28-7.44(m, 4H), 7.92(bs, 2H NH).

Ij (3, 3'-Bis (indolyl)-4-methylphenylmethane)

IR (KBr): 3460, 3020, 1600, 1512, 1456, 1417, 1215, 1091, 1021,762, cm^{-1};
^{1}HNMR ($CDCl_3$): δH 2.34(s, 3H Ar-CH_3), 5.84(s, 1H Ar-CH), 6.68(d, 2H) 7.20-7.40(m, 12H), 7.90(bs, 2H, NH).

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