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A simplified green chemistry approach for synthesis of bis-indolylmethanes using phenylphosphonic acid as an organocatalyst under grinding condition

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Abstract: A simple and efficient method for preparation of bis(indolyl)methanes (BIMs) is described from the electrophilic substitution reaction of indole with aromatic and aliphatic aldehydes in the presence of phenylphosphonic acid as organocatalyst under solvent-free conditions at room temperature by grinding method. This method provides several advantages such as operational simplicity, higher yield and environment friendly.

Keywords: Aldehydes, Bis(indolyl)methanes, Grinding, Solvent-free conditions.

Introduction

Indole fragments are featured wide variety of pharmacologically and biologically active compounds [1]. Among the various indole analogues, bis-indolylmethane derivatives display versatile biological and pharmacological activities [2,3]. 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 [4]. Synthetically, the reaction of 1*H*-indole with aldehydes or ketones produces azafulvenium salts that react further with a second 1*H*-indole molecule to form bis(indol-3 yl)methanes [5]. The synthesis of bis(indol-3-yl)methanes catalyzed by various Lewis acids or protic acids, has previously been reported in literature [6,7]. Most of the reported procedures suffer from disadvantages such as long reaction times [8], low product yields [9], tedious work-up procedure, use of expensive reagents [10], use of a larger stoichiometric amounts of catalyst [11,12], and use of an additional microwave [13] or ultrasound irradiation [14. Consequently, introduction of new methods and catalysts for preparation of BIMs that addresses these drawbacks are desirable. However, there are only a few reports using neutral organic catalysts for this aim [15-17]. In view of that, several synthetic methods for the preparation of BIMs have been reported using catalysts such as $InCl_3$ or $In(OTf)_3$ [18a], TPA-ZrO_2 [18b], $Zr(DS)_4$ [18c], lanthanide triflate [18d], $CuBr_2$ [18e], trichloro-1,3,5-triazine [16], zeolite [4], sulphamic [18f], polyindole salt [18g], $RE(PFO)_3$ [18h], [bnmim][HSO_4] [18i], montmorillonite K10 [18j], iodine [19], *p*-toluenesulfonic acid [20], fluoroboric acid adsorbed on silica gel [21], phosphorus pentoxide/silica gel (P_2O_5/SiO_2) [22], diammonium hydrogen phosphate [23], NH_4Cl [24], ZnO [25a], $Dy(OTf)_3$ [25b], and $H_6P_2W_{18}O_{62}$ [26].

One of the ultimate goals of green chemistry 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 environmentally friendly chemical processes. One way for this purpose is carrying out the reactions under solvent-free conditions [27]. Furthermore, the use of organocatalysts instead of inorganic Lewis acids has some advantages including (i) the possibility of using acid-sensitive substrates and (ii) substrates bearing basic functional groups or electron-donating substituents that are prone

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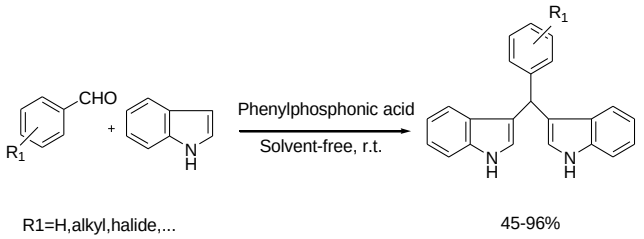
to capture the acidic catalysts do not affect the reaction results [28].

On the other hand, grinding is a valuable method in the view of green chemistry which often leads to a shorter reaction time, increased yields and easier workup which has been considered as a useful protocol in organic synthesis [22].

In this paper, we have reported an efficient method for the preparation of BIMs catalyzed by phenylphosphonic acid as a non-explosive, easy handling, eco-friendly and stable solid acid catalyst by grinding at room temperature (Scheme **1**).



Scheme 1: Synthesis of BIMs catalyzed by phenylphosphonic acid

Results and discussion

Table **1** shows the control experiment of synthesis of BIMs. At the first stage, we examined the synthesis of BIMs using indole (1mmol) and 4-methylbenzaldehyde (0.5 mmol) in the absence of solvent and catalyst as a model reaction and no BIM was produced. Subsequently, the influence of the amount of catalyst on the reaction was examined. As shown in Table **1**, addition of a catalytic amount of phenylphosphonic acid showed a significant effect on the reaction yield and 8 mg (10 mol%) of catalyst was proven to be the optimum amount of catalyst for completion of the reaction.

Table 1: The effect of amount of phenylphosphonic acid on the reaction yield by grinding [a]

Entry	Catalyst (mg)	Time (min)	Yield (%)[b]
1	None	2(h)	N.R.
2	0.0015	20	70
3	0.0031	20	80
4	0.008	4	82
5	0.0158	2	82

[a] Reaction condition: indole (1mmol) and 4-methylbenzaldehyde (0.5 mmol) at room temperature.
[b] Isolated yields.

To explore the diversity of method, the synthesis of various BIMs was investigated by reacting various substituted benzaldehydes and heterocyclic aldehydes with indole at the presence of catalytic amounts of phenylphosphonic acid under solvent-free conditions at room temperature. The results described in Table **2**, indicate the scope and generality of the method. In all cases the reactions are completed in short reaction times and the pure products are obtained in high yields. Aldehydes with electron withdrawing group and electron donating groups were reacted very well and gave corresponding BIMs in excellent yields. Aldehydes with acid sensitive groups such as OMe (Table **2**, entries 3,4) and CN (Table **2**, entry 9) were also converted to BIMs, while their acid sensitive groups remained intact. However, phenylphosphonic acid neutralized by amine group in 4-dimethylamino benzaldeyde, but the reaction proceeds anyway and gives 50% yield in 5h (Table **2**, entry 19). By increasing the catalyst to 0.08g, the yield of the corresponding product was improved and reaction time was shortened (Table **2**, entry 20). As seen in Table **2**, furan-2-carbaldehyde (Table **2**, entry 11) was found to be more reactive than thiophene-2-carbaldehyde (Table **2**, entry 12), giving the corresponding product in excellent yield. Moreover, the required reaction time for the reaction of aromatic aldehydes with electron-withdrawing substituent groups is shorter than electron-donating substituent groups under the same reaction condition.

The present procedure is superior in comparison with $CeCl_3.7H_2O$-catalyzed reaction of benzaldehyde with indole in glycerin at 75ºC [29] which requires longer reaction times. On the other hand, in comparison to some other reported articles for the synthesis of BIMs, eg. using ultrasonic irradiation [30] solvent-free synthesis of BIMs was found to be an excellent choice in terms of reaction condition.

Conclusion

In conclusion, we have described a novel and highly efficient procedure for the preparation of BIMs under solvent-free conditions at room temperature. The procedure offers several advantages including short reaction times, mild conditions, excellent yields, use of an inexpensive and non-toxic catalyst, simple operation and work-up. These advantages make this method as a useful and attractive process for the synthesis of BIMs.

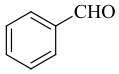
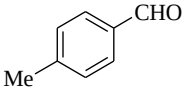
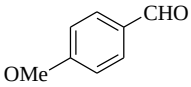
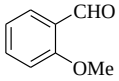
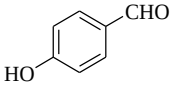
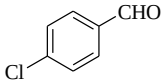
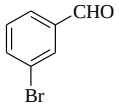
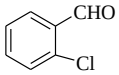
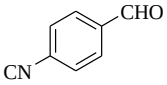
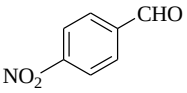
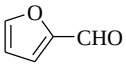
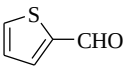
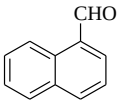
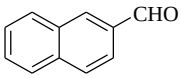
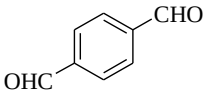
Experimental

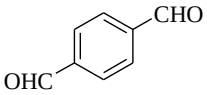
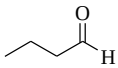
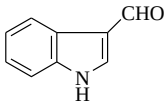
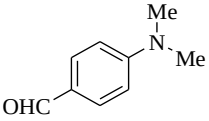
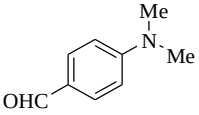
Materials and methods:

All Materials were purchased from Merck. Melting points were measured by using the capillary tube method with an electro thermal 9100 apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded with

Brucker DRX AVANCE (400 MHz) using $CDCl_3$ and DMSO as solvent.

Table 2: Synthesis of BIMs in the absence of solvent [a]

Entry	Aldehyde	Time (min)	Yield (%)[b]	Mp (°C)		Ref.
				Reported	Found	
1		4	90	149-150	148-154	[31]
2		4	82	95-97	97-99	[18e]
3		15	92	185-187	185-187	[31]
4		6	80	131-133	130-132	[34]
5		19	85	123-125	122-124	[32]
6		17	83	104-105	102-105	[32]
7		10	81	140-145	144-145	[32]
8		4	88	70-71	75-77	[19a]
9		7	91	197-199	197-199	[18b]
10		3	96	217-220	218-220	[31]
11		8	96	> 310	325	[33]
12		70	63	150-153	169-171	[18e]
13		8	90	210-212	211-212	[33]
14		8	70	95-98	98-100	[15]
15		2	90	decompose	decompose	[26]

16		8	90	decompose	decompose	[18c]
17		80	45	107-109	105-108	[35]
18		2(h)	N.R.	-	-	-
19		5(h)	50	210-212		[36]
20 [c]		2(h)	90	210-212		[36]

[a] Reaction condition: indole (1mmol), aldehyde (0.5 mmol), catalyst (0.008g) at room temperature.
[b] Isolated yields.
[c] Catalyst (0.08g).

General procedure for preparation of BIMs:

Phenylphosphonic acid (10 mol%, 0.0080 g) was added to a mixture of indole (1mmol) and aldehyde (0.5 mmol) and the mixture was ground using a mortar and pestle for appropriate time at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the crude product was washed with water (3×5mL) to remove the catalyst and subsequently recrystallized from hexane to give almost pure product. The yield and melting points are reported in Table **2**.

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