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Polyvinylpolypyrrolidone-supported triflic acid (PVPP·OTf) as a new, efficient, and recyclable heterogeneous catalyst for the synthesis of bis-indolyl methane derivatives

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ABSTRACT

A simple, inexpensive, environmentally friendly and efficient route for the synthesis of bis-indolyl methane derivatives by the reaction of indole or *N*-methyl indole with aldehydes using polyvinylpolypyrrolidone-supported triflic acid (PVPP·OTf) as a catalyst is described. PVPP·OTf catalyst is air-stable, heterogeneous, cost-effective, easy to handle, and easily removed from the reaction mixtures.

1. Introduction

Organic synthesis using heterogeneous catalysts in the place of homogeneous reagents has received much attention from the standpoint of green and sustainable chemistry because of the possibility of performing environmentally highly acceptable chemical processes [1–4]. The use of heterogeneous catalysts in liquid phase offers several advantages over homogeneous ones, including the ease of recovery and recycling, atom utility, and enhanced stability [5,6]. Triflic acid (TfOH) is widely used as an acid catalyst due to its very strong Brønsted acidity, structure, and properties. Because triflic acid is highly corrosive and it is a fuming liquid, difficulties remain in its storage, transportation, handling, and waste disposal, which severely restricts its application in industry. The immobilization of triflic acid onto an inorganic material, such as silica gel, affords solid acids that can be easily handled, as they invariably are low-toxicity, non-corrosive, free-flowing powders with superior thermal and mechanical stability under catalytic conditions [7].

Different catalytic systems have been studied, in which TFA is adsorbed on various solids, but they are all subject to leaching [8]. Polyvinylpolypyrrolidone displays a strong binding affinity toward small molecules. Furthermore, its iodine complex, povidone–iodine, is widely used as an anti-infective agent in clinical treatments [9]. In continuing our studies on the application of new reagents or systems for organic functional group transformations [10–15], we decided to apply an appropriate method for the synthesis of bis-indolyl methanes derivatives. In this light, we have supported triflic acid on polyvinylpolypyrrolidone to prepare an efficient and mild catalyst for the heterogeneous preparation of bis-indolyl methane derivatives. Bis-indolyl methane derivatives (BIMs) are important biologically active heterocycles. They show antibacterial, anti-inflammatory and antiviral activities [16–20], and can

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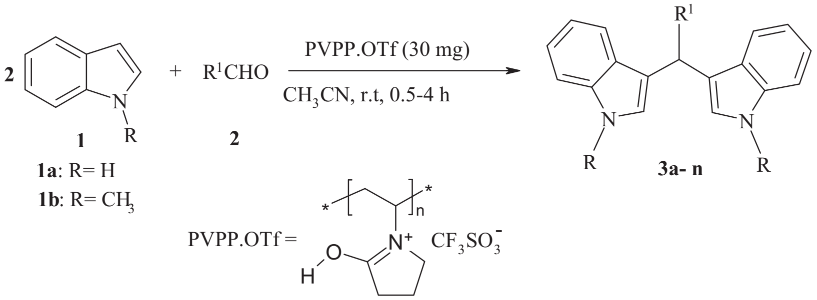


Scheme 1. Synthesis of bis(indolyl)methanes **3** catalyzed by PVPP·OTf.

also be useful in the treatment of fibromyalgia, chronic fatigue and irritable bowel syndrome [21,22], and as dietary supplements for promoting healthy estrogen metabolism in humans [23]. As a result of their biological and synthetic importance, a number of synthetic methods for the preparation of bis(indolyl)alkane derivatives have been reported in the literature by the reaction of indole with various carbonyl compounds in the presence of a catalyst [24–38]. However, some of these procedures have certain limitations, such as high reaction temperatures, prolonged reaction time, the use of toxic solvents, or low yields. The recovery and reusability of the catalyst is also a problem. Therefore, it is still desirable to seek a green and ecofriendly protocol that uses a highly efficient and reusable catalyst for the preparation of bis(indolyl)alkanes. Herein, we found that PVPP·OTf could be used for the preparation of bis(indolyl)alkanes by the reaction of indole or *N*-methyl indole with aldehydes in good to excellent yields (Scheme 1).

2. Results and discussion

In order to optimize the reaction conditions, we chose the condensation reaction of indole with 4-chlorobenzaldehyde catalyzed by PVPP·OTf under different conditions, both in the absence and in the presence of PVPP·OTf; the results are given in Table 1. It is noteworthy that, in the absence of catalyst, the reaction failed to give the desired product, even after long reaction times (24 h, Table 1, entry 1). Then, the effect of temperature, the amount of catalyst, and the reaction time on the yield of the product was examined. Reaction at room temperature (rt) in acetonitrile in the presence of 30 mg of PVPP·OTf afforded the product **3** in 97% yield (Table 1, entry 3). Either increasing the amount of catalyst and/or prolonging the reaction time did not improve the yield (Table 1, entry 9), while reducing these factors led to a reduction in the product yield (Table 1, entry 2). Building upon this result, further studies were conducted, and it was found that 30 mg of PVPP·OTf were optimum for this reaction and gave a product of 97% yield in just 0.5 h (Table 1, entry 3). The reaction was also examined in solvents, such as H_2O, THF, CH_2Cl_2, ethanol, and diethyl ether. In the presence of these solvents, the reaction was sluggish and the formation of the by-products was observed (Table 1, entries 4–8).

Table 1
Effects of the amount of PVPP·OTf catalyst used and of the solvent on the formation of **4**.

Entry	PVPP·OTf amount (mg)	Condition/solvent	Time (h)/yield
1	0	rt/CH_3CN	24/0
2	10	rt/CH_3CN	2/80
3	30	rt/CH_3CN	0.5/97
4	30	rt/CH_2Cl_2	24/20
5	30	rt/THF	24/30
6	30	rt/ethanol	10/70
7	30	rt/H_2O	24/20
8	30	rt/diethyl ether	24/10
9	50	rt/CH_3CN	0.5/97

rt: room temperature.

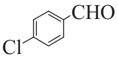
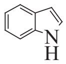
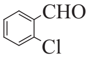
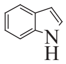
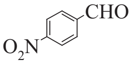
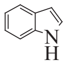
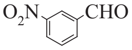
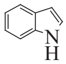
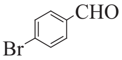
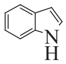
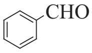
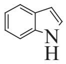
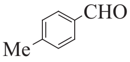
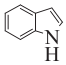
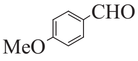
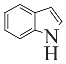
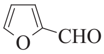
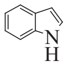
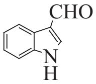
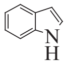
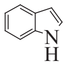
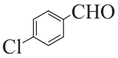
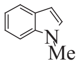
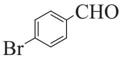
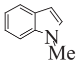
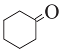
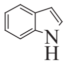
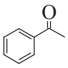
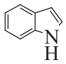
These results prompted us to investigate the scope and the generality of this new protocol for various aldehydes and ketones under optimized conditions (Table 2).

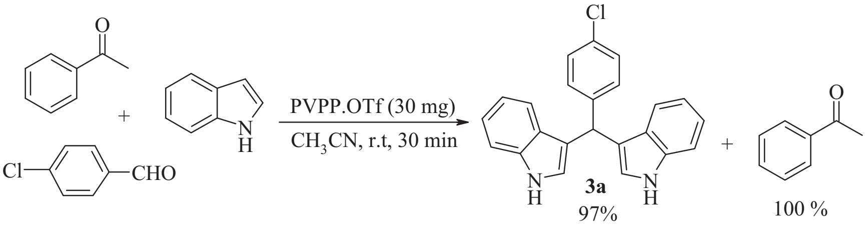
A series of aromatic, aliphatic aldehydes and simple ketones underwent an electrophilic substitution reaction with indole or *N*-methyl indole smoothly to afford a wide range of substituted bis(indolyl)methanes in good to excellent yields (Table 2). This method is equally effective for aldehydes bearing electron-withdrawing or -donating substituents in the aromatic rings. Furthermore, acid sensitive aldehydes worked well without any decomposition or polymerization under these reaction conditions. Also, tris-indolyl methane was produced in excellent yield (Table 2, entry 10). As it is expected, *N*-methyl indole provided better yields of the products in comparison with indole under the same reaction conditions. This method is even effective with aliphatic aldehydes, which normally produce low yields due to their intrinsic lower reactivity. The present method is also highly chemoselective for aldehydes. For example, when a 1:1 mixture of 4-chlorobenzaldehyde and acetophenone was allowed to react with indole in the presence of PVPP·OTf in acetonitrile, it was found that only 4-chlorophenyl-3,3-bis(indolyl)methane (**3a**) was obtained, while acetophenone did not give the corresponding product under these reaction conditions (Scheme 2).

The reactions were clean and the products were obtained in high yields without the formation of any side-products, such as *N*-alkylated ones.

The characterization of the Brønsted acid sites present in the polymer was performed by recording the FT–IR spectrum of PVPP·OTf, which shows a strong broad absorption at 3400 cm^{-1} for the O–H bond and a moderate absorption at 1648 cm^{-1} that corresponds to the internal

Table 2
PVPP·OTf-catalyzed synthesis of BIMs.

Entry	Aldehyde/ketone	Indole	Time (h)	Product	Yield (%)
1			0.5	**3a**	97
2			3	**3b**	96
3			1	**3c**	93
4			2	**3d**	93
5			1.5	**3e**	90
6			1	**3f**	90
7			1.5	**3g**	90
8			2	**3h**	90
9			1	**3i**	96
10			1.5	**3j**	90
11			1	**3k**	85
12			0.5	**3l**	95
13			1	**3k**	95
14			4	**3m**	70
15			4	**3n**	60



Scheme 2. Chemoselectivity of the aldehyde in the reaction with indole in the presence of ketone.

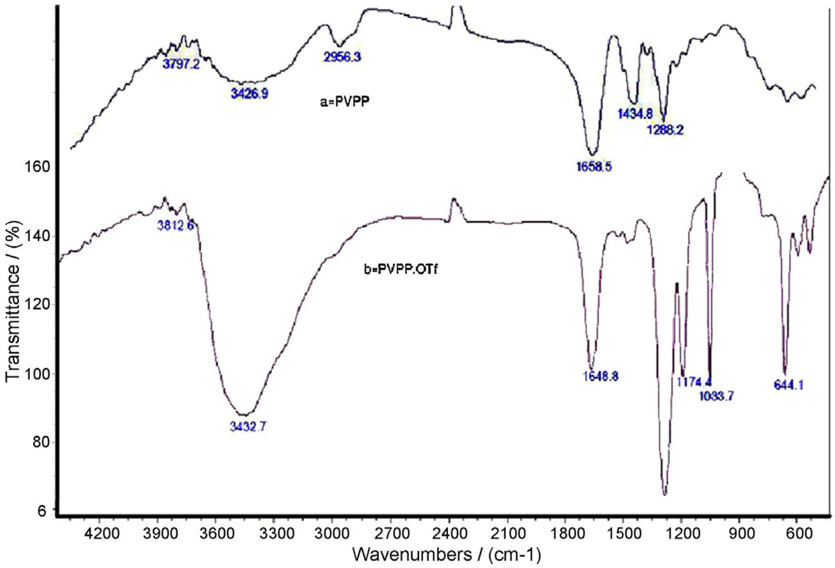


Fig. 1. FT–IR spectrum of polyvinylpolypyrrolidone (PVPP) and (PVPP·OTf) catalyst.

imine groups present in the pendant rings of the polymer (Fig. 1). The loading capacity of the reagent was determined by titration and was found to be 10 mmol/g, whereas its silica-supported analogue has a loading capacity of less than 1 mmol/g.

As PVPP·OTf is not soluble in acetonitrile, no PVPP·OTf leaching as well as no contribution of homogeneous catalysis in the course of reaction was expected. To prove this, after 3 h, the catalyst was removed from acetonitrile by filtration and the supernatant was tested for activity. No activity was observed, indicating that there was no contribution of homogeneous catalysis in this reaction. After the reaction, the catalyst can be easily separated (by filtration) and reused after washing with dichloromethane, with gradual decrease in its activity. For example, the reaction of indole with 4-chlorobenzaldehyde afforded the corresponding bis-indolyl methane derivative in 97%, 95%, and 95% isolated yield over the three cycles.

3. Conclusions

In conclusion, a simple and highly efficient method for the synthesis of bis-indolyl methanes derivatives has been developed via the condensation of indole with aldehydes catalyzed by polyvinylpolypyrrolidoniume triflate in acetonitrile at room temperature. In contrast to the existing methods using potentially hazardous catalysts/additives, the present method offers the following competitive advantages:

- PVPP·OTf is easy to prepare from commercially available polyvinylpolypyrrolidone and triflic acid;
- short reaction time;
- ease of product isolation/purification;
- no side reactions;
- low costs and simplicity in the process and handling;
- bis-indolyl methanes derivatives are produced by an environmentally benign process.

4. Experimental

4.1. Preparation of the polyvinylpolypyrrolidone-supported triflic acid (PVPP·OTf)

To a suspension of polyvinylpolypyrrolidone (3.0 g) in toluene (35 mL), TfOH (2.0 g, 13 mmol) was added. The mixture was stirred magnetically for 60 min at rt. The toluene was removed under reduced pressure and the residue was dried at 110 °C for 2 h to afford PVPP·OTf as a white powder. The number of H^+ sites PVPP·OTf, which was determined by acid–base titration, was 10 mequiv/g.

4.2. Typical experimental procedure

A mixture of aldehyde (1 mmol), indole (2 mmol) dissolved in 4 mL acetonitrile, and PVPP·OTf (30 mg) was stirred for the appropriate reaction time. The reaction was monitored by TLC. After completion of the reaction, the mixture was washed with chloroform and filtered to recover the catalyst. The filtrate was evaporated and dried. The products were characterized by comparison of their physical and spectral data with those of the authentic samples [37]. Spectroscopic data for the selected examples are shown below. Spectroscopic data for the selected examples are as follows.

4.2.1. Bis(3-indolyl)-tolylmethane

Pale–red solid, mp 96–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.31$ (s, 3H), 5.84 (s, 1H), 6.65 (s, 2H), 6.99 (t, 2H, $J = 7.2$ Hz), 7.07 (d, 2H, $J = 8.0$ Hz), 7.15 (t, 2H, $J = 7.6$ Hz), 7.21 (d, 2H, $J = 8.0$ Hz), 7.33 (d, 2H, $J = 8.4$ Hz), 7.38 (d, 2H, $J = 8.0$ Hz),7.86 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$):

$\delta = 21.1$, 39.8, 110.9, 119.2, 119.9, 120.0, 121.8, 123.5, 127.1, 128.5, 128.9, 135.4, 136.7, 141.0 (Table 1, entry 7).

4.3. *Tris (3-indolyl)methane*

Pale yellow solid; mp 160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.07$ (s, 1 H), 6.87 (s, 3H), 6.85 (t, 3H, $J = 7.4$ Hz), 7.03 (t, 3H, $J = 7.2$ Hz), 7.43 (d, 3H, $J = 7.8$ Hz), 7.55 (d, 3H, $J = 7.8$ Hz), 10.72 (s, 3H, –NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.8$, 111.2, 117.8, 118.2, 119.4, 120.5, 123.1, 126.5, 136.4 (Table 1, entry 10).

Acknowledgments

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