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Pentafluorophenylammonium triflate as an efficient, environmentally friendly and novel organocatalyst for 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 pentafluorophenylammonium triflate (PFPAT) as a catalyst is described. PFPAT organocatalyst is air-stable, cost-effective, easy to handle, and easily removed from the reaction mixtures.

1. Introduction

Indoles and their derivatives are the important classes of heterocyclic compounds and are known to possess a wide range of biological activities including antioxidant, antibacterial, and insecticidal activity [1]. Among the various substituted indoles, bis-indolyl methane derivatives (BIMs) are found widely distributed in the bioactive metabolites of terrestrial and marine organisms [2]. BIMs are useful in the treatment of fibromyalgia, chronic fatigue and irritable bowel syndrome [3,4], and as dietary supplements for promoting healthy estrogen metabolism in humans [5], and also effective in the prevention of cancer [6,7]. Consequently, there is an increasing interest in the synthesis of compounds containing bis(indolyl)alkanes moiety. Over a past few years, several catalyst systems have been reported, such as lanthanide triflates [8], $InCl_3$ [9], $LiClO_4$ [10], Zn^{2+} ion-exchanged Y zeolite [6], montmorillonite K10 clay [11], ionic liquids with $FeCl_3$ [12], $NaHSO_4{\cdot}SiO_2$/Amberlyst 15 [13], Zeokarb-225 [14], $HClO_4$–SiO_2 [3], macroreticular FPS resins [15], SBA-15-supported poly(4-styrenesulfonyl (perfluorobutylsulfonyl)imide) [16], $H_3PW_{12}O_{40}$ [17], $Zr(DS)_4$ [18], Pyridinium tribromide [19] and $Zr(Cl_4)$ [20]. However aforementioned developed methods suffer from the following disadvantages such as: expensive or unavailability or toxicity of the reagent, extended reaction times, additionally the main drawback of almost existing methods is that the catalysts are decomposed under aqueous work-up conditions and their recoveries are often impossible. Furthermore, these methods are not suitable in terms of the recent trends in process chemistry, due to the use of metallic catalysts. Therefore, a method using a nonmetallic catalyst is desirable. In recent years, organocatalysis using small molecules has generated considerable interest as a viable tool for asymmetric and non-asymmetric synthesis over the last half a decade [21]. Novel methods employing organic molecules are advantageous from both a practical and an environmental standpoint due to their ability to perform in wet solvents under an aerobic atmosphere and to avoid the possibility of metal contamination that may occur with traditional metal catalyst systems. Recently, pentafluorophenylammonium triflate ($C_6F_5N^+H_3{\cdot}OTf^-$; PFPAT) has received increasing attention as a water-tolerant Brønsted acid catalyst for organic synthesis demonstrating highly chemo-, regio- and stereoselective results [22]. Compared to conventional Lewis acids, it has advantages of water stability, recyclability, operational simplicity, strong tolerance to oxygen and nitrogen-containing substrates and functional groups, and it can often be used in catalytic amounts. In continuation of our investigations on the development of new synthetic methodologies [23], we herein report a new, convenient, mild and efficient procedure for the synthesis of BIMs derivatives by the reaction of Indole or *N*-methyl indole with aldehydes in the presence of pentafluorophenylammonium triflate (PFPAT) as an effective and novel organocatalyst under mild reaction conditions (Scheme 1).

2. Results and discussion

To initiate our study, the reaction of indole with 4-chlorobenzaldehyde was chosen as a model reaction in the presence of PFPAT

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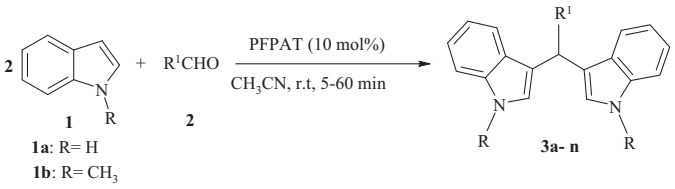


Scheme 1.

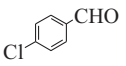
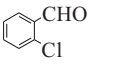
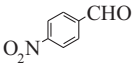
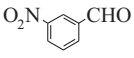
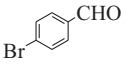
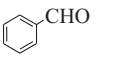
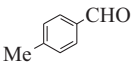
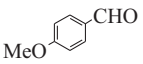
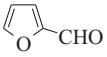
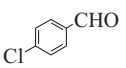
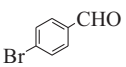
(10 mol%) in acetonitrile at room temperature. The corresponding bis(indolyl)methanes **3a** was obtained in high yield (97%) after 10 min (Table 1, entry 1). These results prompted us to investigate the scope and the generality of this new protocol for various aldehydes and ketones under optimized conditions (Table 1).

A series of aromatic, aliphatic aldehydes and simple ketones underwent electrophilic substitution reaction with indole and *N*-methyl indole smoothly to afford a wide range of substituted bis(indolyl)methanes in good to excellent yields (Table 1). 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 1, entry 10). As it is expected, *N*-methyl indole provided better yields of products in compare 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. This 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 HFIP 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 this 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 product. Selective condensation of a dialdehyde i.e. terephthaldialdehyde to the corresponding bis-indolyl methane was achieved by controlling the molar ratio of indole (Scheme 3). The results showed that the addition of 2 equiv. of indole to terephthaldialdehyde, gives **3o** in 90% yield (Scheme 3). Treatment of 4 equiv. of indole with terephthaldialdehyde gives the corresponding di(bis-indolyl methanes), **3p**, respectively, in high yields at room temperature in acetonitrile (Scheme 3).

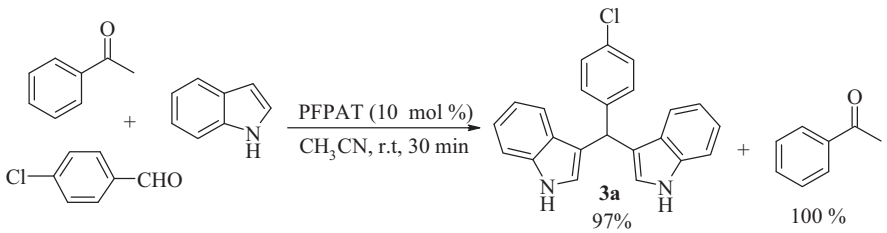
In addition, the PFPAT catalyst was easily separated from the reaction mixture after work-up; washing with NaOH aqueous solution removed CF_3SO_3H, followed by distillation under reduced pressure ($C_6F_5NH_2$: bp 153 °C at 760 mmHg).

Table 1
PFPAT catalyzed synthesis of BIMs.

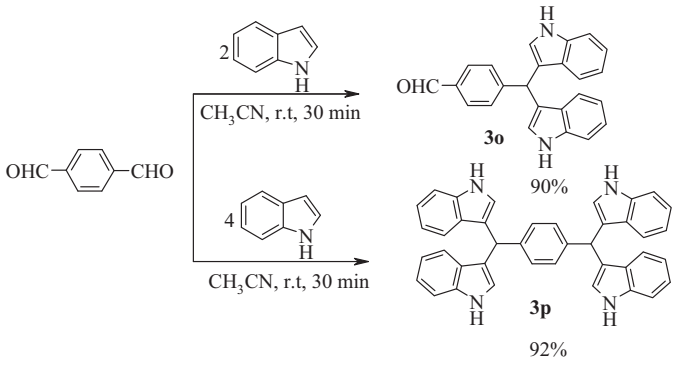
Entry	Aldehyde/ketone	Indole	Time (min)	Product	Yield % [Ref.]
1			10	**3a**	97 [17]
2			15	**3b**	97 [19]
3			8	**3c**	96 [17]
4			10	**3d**	98 [17]
5			15	**3e**	90 [17]
6			20	**3f**	90 [19]
7			20	**3g**	95 [19]
8			25	**3h**	95 [19]
9			10	**3i**	96 [19]
10			20	**3j**	95 [18]
11			25	**3k**	90 [19]
12			5	**31**	95 [18]
13			5	**3k**	95 [18]
14			45	**3m**	90 [17]
15			60	**3n**	60 [17]

3. Conclusions

In conclusion, a simple and highly efficient method for the synthesis of bis-indolyl methane derivatives has been developed



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



Scheme 3.

via condensation of indole with aldehydes catalyzed by Pentafluorophenylammonium 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: (i) PFPAT is easy-to prepare from commercially available pentafluoroaniline and triflic acid, (ii) short reaction time, (iii) ease of product isolation/purification, (iv) no side reaction, (v) low costs and simplicity in process and handling and (vi) bis-indolyl methane derivatives are produced by an environmentally benign process.

4. Experimental

4.1. Typical experimental procedure

A mixture of aldehyde (1 mmol), indole (2 mmol) dissolved in 3 mL acetonitrile, and PFPAT (10 mol%) was stirred for appropriate reaction time. The reaction was monitored by TLC. After cooling to room temperature, the organic phase was washed with 1 M NaOH aqueous solution (1 mL). The separated organic phase was evaporated under reduced pressure to give a crude product, which was purified by distillation or by column chromatography (hexane–ethyl acetate). Products were characterized by the comparison of their physical and spectral data with those of authentic samples. Spectroscopic data for selected examples follow:

Bis(3-indolyl)-tolylmethane (Table 1**, entry 7)**: Pale-red solid; mp 96–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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.

Tris (3-indolyl)methane (Table 1**, entry 10)**: Pale yellow solid; mp 160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.07 (s, 1H), 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, $CDCl_3$): δ = 30.8, 111.2, 117.8, 118.2, 119.4, 120.5, 123.1, 126.5, 136.4.

3,3′,3″,3‴-Tetraindolyl(terephthalyl)dimethane (Scheme 3**, 3p)**: Pink solid; mp 194 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (s, 2H), 6.29 (s, 4H), 7.05 (t, 4H, J = 7.6 Hz), 7.16 (t, 4H, J = 7.6 Hz), 7.24–7.40 (m, 12H), 7.31 (br s, 4H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.2, 111.6, 118.2, 118.4, 119.3, 120.8, 123.4, 126.8, 128.2, 136.7, 142.5.

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