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Facile synthesis of bis(indolyl)methanes using iron(III) phosphate

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Abstract: A new, convenient and high yielding procedure for the preparation of bis(indolyl)methanes in glycerol by the electrophilic substitution reaction of indole with aldehydes in the presence of catalytic amount of $FePO_4$ (5.0 mol %) as a highly stable and reusable catalyst is described.

Keywords: $FePO_4$; synthesis; bis(indolyl)alkanes; aldehyde; glycerol; catalyst.

INTRODUCTION

Lewis acids accelerate a wide range of organic reactions by binding to and thereby activating reactants. This activation often results in rate increases of many orders of magnitude compared with the thermal reaction. Transition metal Lewis acids are promising and interesting because the precursor is often structurally well-defined and steric and electronic tuning of the ligand to a particular reaction is facilitated. Iron(III) phosphate as a Lewis acid has been employed as a catalyst for the transformation of various organic functional group under heterogeneous conditions, such as the selective oxidation of CH_4 to CH_3OH,[1] benzene to phenol,[2] one-pot synthesis of dihydropyrimidinones and thiones,[3] synthesis of triarylated imidazoles,[4] acetylation of alcohols and phenols,[5] tetrahydropyranylation and tetrahydrofuranylation of alcohols and phenols,[6] synthesis of 2-substituted benzimidazoles,[7] and synthesis of polyhydroquinoline derivatives.[8]

Furthermore, the structural motifs of indole derivatives are found in numerous biologically active compounds, which are used as anti-oxidants and pharmaceuticals.[9–13] Bis(indolyl)alkanes are present in many biologically active natural products and are known to have applications in research areas, such as pharmaceuticals and materials science.[14–20] Consequently, there is an increased interest in the synthesis of compounds containing bis(indolyl)alkanes moieties due to their importance and a number of synthetic methods for the synthesis of bis(in-

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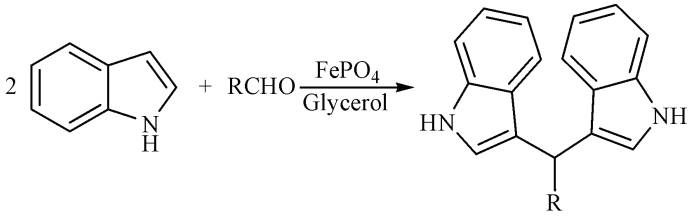
dolyl)alkanes have been described in the literature.[21–24] However, the procedures described in the literature to access bis(indolyl)alkanes are mainly focused on the condensation of indole with carbonyl compounds in the presence of a protic acid or a Lewis acid. Also, The synthesis of bis(indolyl)alkanes by the reaction of indoles with alkynes catalyzed using $Cu(OTf)_2$ has also been reported.[25]

Lately, glycerine, which is readily available as a co-product in the production of biodiesel, has attracted attention as a versatile, cheap and renewable feedstock in synthetic organic chemistry.[26,27] In view of current interest in catalytic processes, the development of a method for the synthesis of bis(indolyl)methanes using inexpensive, mild and non-polluting reagents is highly desirable. The introduction of reusable catalysts is preferred in order to minimize environmental pollution due to the usage of hazardous solvents and their disposal. The limitations of the current methods, together with the demand for greener alternatives prompted us to develop a new method for the synthesis of bis(indolyl)methanes.

Due to our interest in developing new methodologies in catalytic organic syntheses and to show the versatility of iron(III) phosphate in organic synthesis,[1–8] the preparation of bis(indolyl)methanes by reaction of indole with aldehydes in the presence of a catalytic amount of $FePO_4$ (5.0 mol %), as an inexpensive, eco-friendly and reusable catalyst, in glycerol at 75 °C (Scheme 1) is described herein.



Scheme 1. The preparation of bis(indolyl)methanes by reaction of indole with aldehydes in the presence of a catalytic amount of $FePO_4$.

EXPERIMENTAL

Melting points were measured by the capillary tube method using an Thermo Scientific electrothermal 9200 apparatus. The IR spectra were recorded on a Perkin Elmer FT-IR spectrometer in the wavenumber range 4000–400 cm^{-1}. ^{1}H-NMR spectra were obtained on Bruker DRX-300MHZ NMR instrument. Chemicals shifts are reported in parts per million (δ) relative to tetramethylsilane (δ = 0.0 ppm) as internal standard. GC/mass spectra were recorded on an Agilent 6890 GC Hp-5 capillary 30 m×530 μm×1.5 μm nominal operating at 70 eV. Analytical TLC of all reactions was performed on Merck pre-coated plates (silica gel 60F-254 on aluminium). All starting materials purchased from Merck Co. All products were characterized by ^{1}H-NMR, FT-IR, and comparison of their melting points with authentic samples.

*Synthesis of 3,3'-bis(indolyl)phenylmethane (**1**)*

The reaction of benzaldehyde (1 mmol) and indole (2 mmol) was used as a model reaction to determine the optimal conditions for the preparation of bis(indolyl)methanes. The

effect of varying the amount of $FePO_4$ (0–10 mol %) was studied by stirring the reactants in 4 mL glycerol for 3 h at 75 °C (Table I) After completion of the reaction (monitored by TLC), the mixture was treated with ethyl acetate and the catalyst filtered off. After evaporation of the solvent, the residue was collected and purified by recrystallization from ethanol. Using the optimal concentration (5 mol %) of $FePO_4$, the synthesis was repeated for the same time at the same temperature but in different solvents (Table II). Finally, the synthesis was performed in glycerol using the optimal concentration of $FePO_4$ by stirring for 3 h at different temperatures (25–80 °C) (Table III).

TABLE I. Effect of varying the amount of catalyst on the yield of 3,3'-bis(indolyl)phenylmethane; benzaldehyde, 1.0 mmol, indole, 2.0 mmol, glycerol, 4.0 mL at 75 °C

Entry	Catalyst, mol %	τ / h	Yield, %
1	–	3.0	10
2	2.0	3.0	60
3	5.0	3.0	90
4	10	3.0	90

TABLE II. Effect of the solvent on the yield of 3,3'-bis(indolyl)phenylmethane; benzaldehyde, 1.0 mmol, indole, 2.0 mmol, at 75 °C in 3.0 h

Entry	Solvent (4.0 mL)	Yield, %
1	Glycerol	90
2	EtOH	70
3	H_2O	60
4	EtOH/H_2O	65
5	–	60

TABLE III. Synthesis of 3-[(1*H*-indol-3-yl)phenylmethyl]-1*H*-indole using $FePO_4$ in glycerol at different temperatures

Entry	t / °C	τ / h	Yield, %
1	25	3.0	30
2	50	3.0	65
3	75	3.0	90
4	80	3.0	90

*Synthesis of 3,3'-bis(indolyl)methane (**2**–**15**)*

Compounds **1**–**14**, Table IV, were prepared by reaction of indole (2 mmol) with the required aldehyde (1 mmol) in 4 mL glycerol at 75 °C in the presence of 5 mol % $FePO_4$. After completion of the reaction, controlled by TLC (the reaction times are given in Table IV), ethyl acetate was added, the catalyst filtered off and the solvent evaporated. The residue was recrystallized from ethanol to afford the pure compound.

Reusability of the catalyst

To test its reusability, the catalyst recovered by gravity filtration at the end of the reaction was washed with ethyl acetate and reused for 5 sequential preparations of compound **1**.

TABLE IV. $FePO_4$ catalyzed synthesis of bis(indolyl)methanes

Entry	Aldehyde	τ / h	Yield, %	M.p. / °C (found)	M.p. / °C (reported)	Ref.
1	Benzaldehyde	3	90	125	123–126	31
2	2-Chlorobenzaldehyde	8	80	72	69–71	30
3	4-Chlorobenzaldehyde	8	85	75	76–78	30
4	*Trans*-Cinnamaldehyde	7	85	100	95–97	29
5	2-Methoxybenzaldehyde	5	93	138	134–136	28
6	4-Methoxybenzaldehyde	4	92	176	178–181	28
7	3,4-Dimethoxybenzaldehyde	5	84	195–198	198–199	31
8	4-Methylbenzaldehyde	5	84	64–98	97–99	28
9	4-Dimethylaminobenzaldehyde	7	75	208–220	210–212	29
10	2-Hydroxybenzaldehyde	5	75	350	340–342	30
11	4-Hydroxybenzaldehyde	6	87	150	120–123	30
12	4-Nitrobenzaldehyde	5	84	220	216–218	32
13	Hexanal	7	76	65	67–74	30
14	Butanal	6	75	80	73–75	32
15	Furfural	8	90	340–345	322–324	29

RESULTS AND DISCUSSION

To the best of our knowledge, the preparation of bis(indolyl)methanes catalyzed by anhydrous iron(III) phosphate has not been reported previously.

The main aim of this work was to provide a new catalytic and environmentally benign protocol for the synthesis of bis(indolyl)methanes. Herein, a simple and fast method for the synthesis of bis(indolyl)methanes in glycerol using $FePO_4$ is reported.

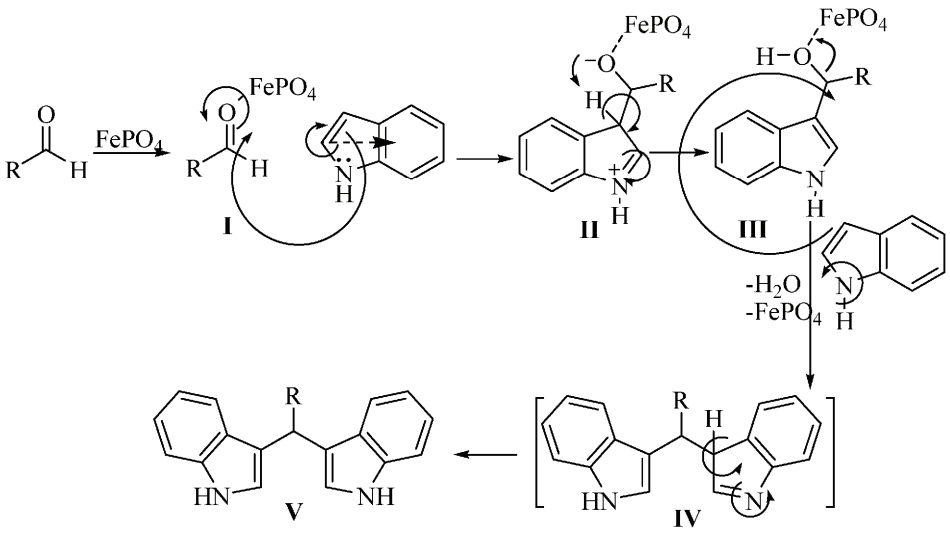
To establish the optimum condition for this reaction, various ratios of $FePO_4$ were examined using indole and bezaldehyde in glycerol at 75 °C as a model reaction (Table I). It can be seen that very little of the desired product was obtained in the absence of catalyst and the best yields were obtained with $FePO_4$. Thus, the catalyst is an essential component for the synthesis of bis(indolyl)methanes by the reported method.

Then the effect of the solvent was examined using different solvents in the model reaction, whereby different yields were obtained (Table II). Obviously, glycerol stands out as the solvent of choice with its fast reaction rate, high yield, selectivity, cheapness and environmental acceptability.

The effect of temperature was investigated by performing the model reaction in glycerol and at different temperatures (25, 50, 75 and 80 °C). It was observed that the yield is a function of temperature with the yield increasing with increasing reaction temperature up to 75 °C. Thereafter, no further increase in the yield was registered. Therefore, all further reactions were performed in glycerol at 75 °C (Table III).

To evaluate the scope and limitations of this work, different bis(indolyl)methanes were synthesized using aliphatic, heterocyclic and aromatic aldehydes (Scheme 1, Table IV). As can be seen in Table IV, the aromatic and heterocyclic aldehydes reacted similarly to give the corresponding bis(indolyl)methanes in high yields and relatively short reaction times. The aliphatic aldehydes reacted smoothly providing the corresponding products in good to moderate yields (entries **4**, **14** and **15**).

This condensation reaction probably proceeds through the activation of a carbonyl group by $FePO_4$ as a Lewis acid to give intermediate **I**, which is followed by indole attack of **I** to give **II**. After proton rearrangement to give **III**, the other indole is added to **III** with the loss of $FePO_4$ and H_2O to afford **IV**, with the following step resulting in the product **V** (Scheme 2).



Scheme 2. Suggested mechanism for the synthesis of bis(indolyl)methanes

At the end of the reaction, the catalyst was recovered by gravity filtration and recycled after washing with ethyl acetate and employed for further preparations. The results showed that the yield of product after five runs was only slightly reduced.

CONCLUSION

In conclusion, $FePO_4$ in glycerol was found to be mild and effective catalyst for the electrophilic substitution reactions of indole with aldehydes, giving bis(indolyl)methanes in excellent yields. The use of this inexpensive and easily available catalyst under mild conditions, the clean reaction and greater selectivity make this protocol practical and economically attractive. The procedure was

found to be general as a variety of aldehydes reacted with indole under mild reaction conditions.

SUPPLEMENTARY MATERIAL

Physical and spectral data of the synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

И З В О Д

ЛАКА СИНТЕЗА БИС(ИНДОЛИЛ)МЕТАНА ПОМОЋУ ГВОЖЂЕ(III)-ФОСФАТА

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Описан је нов поступак за синтезу бис(индолил)метана реакцијом индола и алдехида, у глицеролу у присуству каталитичких количина $FePO_4$ (5,0 mol %). Производи се добијају у високом приносу а катализатор је стабилан и може се користити више пута.

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