

# Titania (TiO<sub>2</sub>)-Catalyzed Expedient, Solventless and Mild Synthesis of Bis(Indolyl)Methanes

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Received: 13-03-2007

## Abstract

Titania (TiO<sub>2</sub>) is found to be an efficient catalyst for the electrophilic substitution reaction of indoles with aldehydes to afford the corresponding bis(indolyl)methanes in high yields under solvent free conditions.

**Keywords:** Titania, aldehydes, bis(indolyl)methane, indole

## 1. Introduction

Bis(indolyl)alkanes and their derivatives constitute an important group of bioactive metabolites of terrestrial and marine origin.<sup>1</sup> During the last few years a large number of natural products containing bis(indolyl)methanes<sup>2</sup> and bis(indolyl)ethanes<sup>3</sup> have been isolated from marine sources. Indoles and their derivatives are used as antibiotics.<sup>4</sup> The acid catalyzed reaction of electron rich heterocyclic compounds with *p*-dimethylaminobenzaldehyde is known as the Ehrlich test<sup>5</sup> for electron rich heterocycles, such as pyrroles and indoles. The analogous reaction of indoles with other aromatic or aliphatic aldehydes and ketones produces azafulvenium salts. The azafulvenium salts can undergo further addition with a second indole molecule to afford bis(indolyl)methanes.<sup>6</sup> Protic acids<sup>7</sup> as well as Lewis acids<sup>8,9</sup> are known to promote these reactions. Recently montmorillonite clay K-10<sup>10</sup> and lanthanide triflates<sup>11</sup> have been also found to catalyze these transformations. However, many Lewis acids become deactivated or sometimes decomposed by nitrogen containing reactants. Even when the desired reactions proceed, more than stoichiometric amounts of the Lewis acids are required because the acids are trapped by nitrogen.<sup>12</sup> These problems can be somewhat circumvented by using expensive lithium perchlorate.<sup>13</sup> However, longer reaction

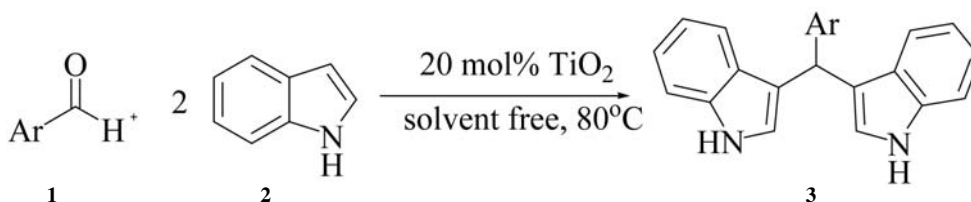
times and moderate to poor yields for nitro-substituted aromatic aldehydes are the limitations.

The use of metal oxides as catalysts has received considerable attention in organic synthesis due to their environmental compatibility, ease of handling, non-toxic nature and above all their reusability and the development of solvent-less protocol has an added advantage in green context. Recently, titania (TiO<sub>2</sub>) has been used as a solid catalyst in many organic transformations.<sup>14</sup> To my knowledge all the catalysts and reagent which are useful for the synthesis of bis(indolyl)methanes are acids (Lewis or protic acids) and there are not any reports for such reaction in the presence of a neutral catalyst.

## 2. Results and Discussion

Herein and according to our previous works aimed at solvent-less procedures,<sup>15</sup> I wish to report the use of a catalytic amount of TiO<sub>2</sub> as a reusable and neutral solid catalyst for the synthesis of bis(indolyl)methanes (Scheme 1).

Firstly, benzaldehyde was chosen as a model for the reaction with indole. Benzaldehyde (**1a**) was treated with 2 mmol of indole (**2**) with various amounts of TiO<sub>2</sub> and under various conditions (Table 1). The best result was



Scheme 1

obtained when 20 mol% of TiO<sub>2</sub> has been used in solvent free conditions (entry 1).

**Table 1:** Effect of reaction conditions on the TiO<sub>2</sub> catalyzed reaction of benzaldehyde (1 mmol) with indole (2 mmol)

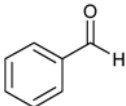
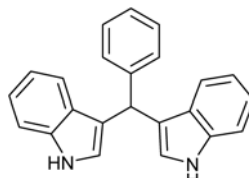
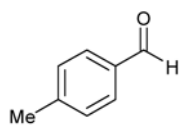
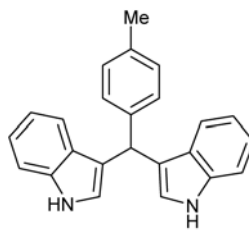
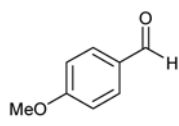
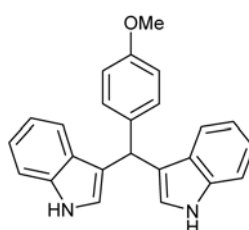
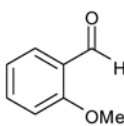
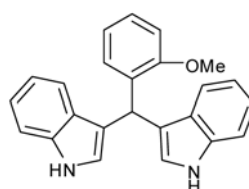
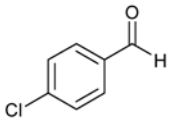
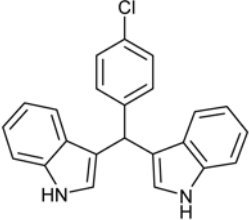
Entry	Catalyst	Solvent	Time (h)	Yield (%) <sup>a)</sup>
1	20% TiO <sub>2</sub>	None	3	95
2	10% TiO <sub>2</sub>	None	5	90
3	5% TiO <sub>2</sub>	None	7.5	90
4	20% TiO <sub>2</sub>	CH <sub>3</sub> CN	12	10
5	20% TiO <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	12	trace
6	20% TiO <sub>2</sub>	EtOAc	12	trace

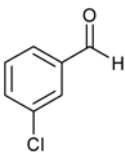
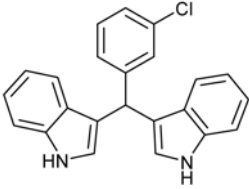
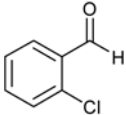
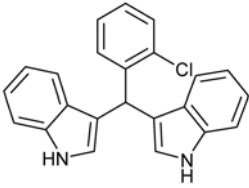
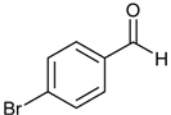
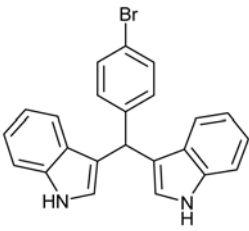
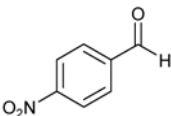
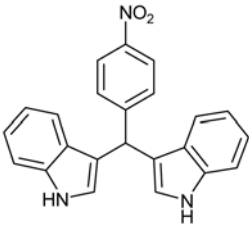
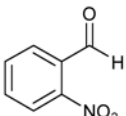
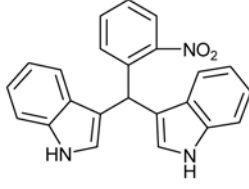
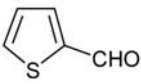
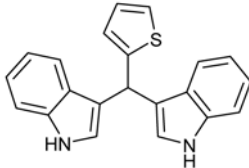
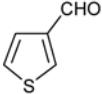
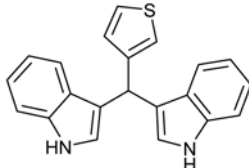
<sup>a)</sup> Isolated yields.

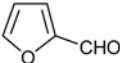
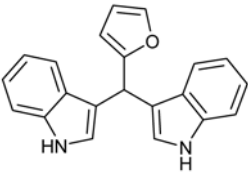
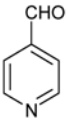
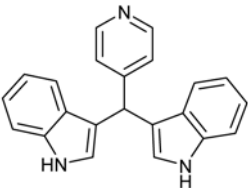
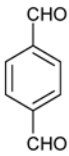
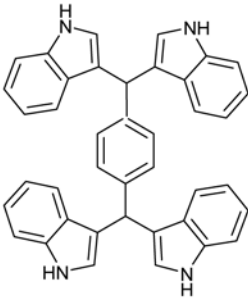
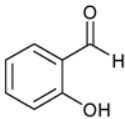
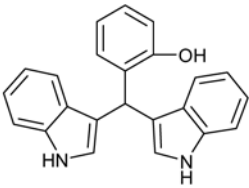
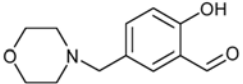
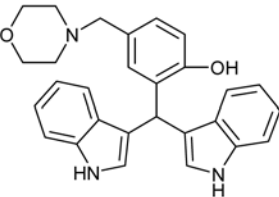
To prove the generality of the protocol, the reaction was then extended towards a variety of aldehydes **1b–q** with indole and the results are summarized in Table 2.

The methodology is found to be general as the reactions of a variety of substituted aromatic aldehydes (**1a–j**) as well as heterocyclic (**1k–n**), with indoles have furnished the corresponding bis(indolyl)methanes in excellent yields. In this context, the present protocol is noteworthy because even nitro substituted aromatic aldehydes (**1i,j**) underwent smooth reactions with indole giving excellent yields of products under mild conditions. It is also interesting to note that even the reaction of indole with terephthalaldehyde (**1o**) under this reaction condi-

**Table 2:** TiO<sub>2</sub>-catalyzed synthesis of bis(indolyl)methanes **3**<sup>a</sup> by condensation reaction of indole with aldehydes **1**

Entry	Aldehyde <b>1</b>	Product <b>3</b>	Time (h)	Yield (%) <sup>b</sup>
a			3	98
b			5	90
c			5.5	95
d			6	95
e			7.5	90

Entry	Aldehyde 1	Product 3	Time (h)	Yield (%) <sup>b</sup>
f			7	95
g			7	90
h			6.5	90
i			7.5	91
j			8	84
k			4	80
l			4.5	84

Entry	Aldehyde 1	Product 3	Time (h)	Yield (%) <sup>b</sup>
m			8	72 <sup>c</sup>
n			5	82
o			4.5	85
p			6	93
q			12	61

<sup>a)</sup> All products, except **3q** are known and were characterized by <sup>1</sup>H NMR, IR and mass spectral data which were found to be identical with those described in ref. 16: for compounds **3a–c**, **3e**, **3g**, **3i**, **3k**, **3m** and **3o** see 16a, for **3d**, **3f**, **3j**, and **3p** see 16b, for **3l** see 16c and for **3h**, and **3n** see 16d. <sup>b)</sup> Isolated yields. <sup>c)</sup> The reaction was done at room temperature.

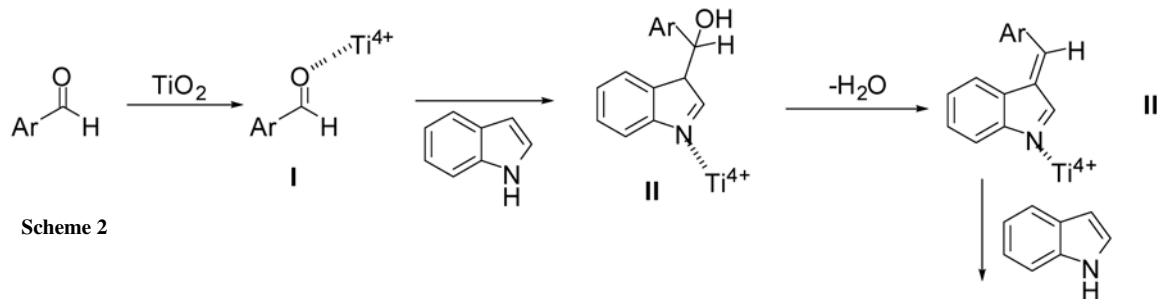
tion furnished the corresponding tetra(indolyl)methane derivative **3o** in excellent yield. It is important to note that heterocyclic aldehydes **1k–n** underwent smooth reactions with indole giving excellent yields of the corresponding bis(indolyl)methanes under mild conditions, especially in the case of acid sensitive compound **1m**, a

reaction otherwise problematic under highly acidic conditions.

To check the reusability of the catalyst, when the reaction of indole with benzaldehyde **1a** was finished, the product formed was extracted with EtOAc and the catalyst was filtered. It was washed with water repeatedly,

dried and reused for the reaction of indole with the same or different aldehydes. It was found that catalyst can be recycled for at least eight cycles without any change in activity.

According to the literature data,<sup>17</sup> I think that  $\text{TiO}_2$  catalyzes the reaction as a mild Lewis acid even under solvent-free conditions.  $\text{TiO}_2$  has (i)  $\text{Ti}^{4+}$  site, which is of Lewis-acid type, (ii)  $\text{O}^{2-}$  site, which is of Lewis-base type, and (iii) surface  $-\text{OH}$  groups.<sup>18</sup> The activation of carbonyls through hydrogen bonding by Lewis acids is also known.<sup>19</sup> So, I propose a mechanism for this reaction using  $\text{TiO}_2$  as shown in Scheme 2. The Lewis acid moiety ( $\text{Ti}^{4+}$ ) activates the carbonyl groups to give intermediate **I** and is followed by indole attack to **I** to give **II** and loss of  $\text{H}_2\text{O}$  from **II** to afford **III** which is activated by  $\text{TiO}_2$ . The other indole is added to **III** in the following step to give the final product **3**.



Scheme 2

### 3. Experimental

Progress of the reactions was monitored by the use of silica gel polygrams SIL G/UV 254 plates. IR spectra were recorded on Perkin Elmer 781 and on Impact 400 D Nicolet FTIR spectrometers. NMR spectra were recorded on Bruker DPX 250 MHz instrument and mass spectra on Shimadzu QP 1100 EX spectrometer using EI 70 eV modes.

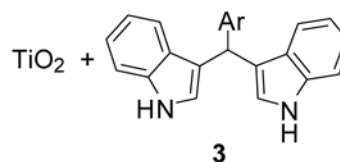
#### 3.1. General Procedure

A mixture of  $\text{TiO}_2$  (0.016 g, 0.2 mmol), benzaldehyde (1 mmol) and indole (0.2 g, 2 mmol) was added to a test tube and heated in an oil bath at 80 °C with stirring. The progress of the reaction was monitored by TLC (hexane : EtOAc = 80 : 20). After the reaction was completed, the catalyst was filtered, following by washing with ethyl acetate (3 × 30 ml). The volume was concentrated under reduced pressure and the product was purified by column chromatography (hexane : EtOAc = 80 : 20).

**2-[Di(1*H*-indol-3-yl)methyl]phenol (3p):** Yield 93%, oil,  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ) 5.82 (s, 1H, CH), 6.50 (brs, 1H,  $-\text{OH}$ ), 6.59 (s, 2H, 2 × NH), 6.89 (t, 2H,  $J$  = 6.5 Hz, Ar-H), 7.03–7.09 (m, 2H, Ar-H), 7.11–7.23 (m,

6H, Ar-H), 7.45 (d, 2H,  $J$  = 7.8 Hz, Ar-H), 7.64 (s, 2H, Ar-H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) 29.8, 111.3, 117.6, 119.5, 120.0, 120.8, 122.3, 124.5, 126.8, 127.9, 129.5, 130.1, 136.8, 137.2, 154.4. Mass (ES/MS):  $m/z$  338 ( $\text{M}^+$ , 100%). Anal. Calcd. for  $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}$ : C 81.63, H 5.36, N 8.28. Found: C 81.78, H 5.42, N 8.32.

**2-[Di(1*H*-indol-3-yl)methyl]-4-(4-morpholinylmethyl)phenol (3q):** Yield 61%, yellow oil,  $^1\text{H}$  NMR (250 MHz,  $\text{DMSO}-d_6$ ) 1.94 (s, 4H, 2 × N- $\text{CH}_2$ ), 2.98 (s, 2H,  $\text{CH}_2$ ), 3.28 (s, 4H, 2 × O- $\text{CH}_2$ ), 5.99 (s, 1H, CH), 6.53 (s, 2H, 2 × NH), 6.60–7.33 (m, 13H, Ar-H), 10.42 (br s, 1H, OH).  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ) 31.8, 52.3, 59.7, 66.1, 11.2, 118.7, 119.2, 120.6, 120.8, 123.5, 124.8, 126.8, 127.3, 130.1, 130.4, 136.6, 152.2, 153.3. Mass (ES/MS):  $m/z$  437 ( $\text{M}^+$ , 100%). Anal. Calcd. for  $\text{C}_{28}\text{H}_{27}\text{N}_3\text{O}_2$ : C 76.86, H 6.22, N 9.60. Found: C 76.95, H 6.30, N 9.72.



### 4. Conclusions

In summary, a simple, convenient, environmentally friendly and efficient synthetic protocol for the synthesis of **3**, using a catalytic amount of  $\text{TiO}_2$  under solvent free conditions has been developed. High yields, use of very safe and cheap catalyst and the simplicity of the reaction procedure make this method one of the most efficient methods for the synthesis of this class of compounds.

### 5. Acknowledgment

I gratefully acknowledge the support of this work by the Shiraz University. I am also grateful to Prof. H. Sharghi for synthesis of aldehyde **1q** and his helpful cooperation.

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## Povzetek

Titanov dioksid (TiO<sub>2</sub>) učinkovito katalizira elektrofilne substitucije indolov z aldehydi. Pri teh reakcijah, ki potekajo brez dodanih topil, z visokimi izkoristki nastanejo ustrezni bis(indolil)metani.