La $(OTf)_3$: An efficient catalyst for green synthesis of bis (Indolyl)methanes under solvent free conditions.

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Abstract

An efficient, mild and inexpensive La$(OTf)_3$ catalyst was used for the synthesis of bis(indolyl) methane derivatives from indole and aromatic aldehydes under microwave irradiation. The yield of product formation using such process afforded excellent yields as compare to conventional method. We believed the methodology is simple, high yielding and environmentally friendly.

Keywords: Indole, aldehydes, La(OTf)3, Solvent-free.

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Introduction

Indole and their derivatives constitute an important class of biologically active natural products, which play a fundamental role in bioorganic chemistry. Indole usually obtained in small amounts by the extraction of naturally occurring materials. Various plants contain certain amount of indole including, Robinia pseudacacia, jasmines, certain citrus plants and orange blossoms [1] etc. These compounds are important intermediates in organic synthesis and exhibit various physiological and pharmacological activities, such as beneficial estrogens metabolism promoter, human prostate cancer cell growth inhibitors [2] and radical scavenging activities associated with cancer cells [3].

Over the past decade, number of natural products containing bis(indolyl)methanes (BIMs) have been isolated from marine sources indeed [4]. To achieve facile and efficient production of this group of indoles several Bronsted acids (e.g. HCl, H_2SO_4) [5], $LiClO_4$ [6], $In(OTf)_3$ [7], $Dy(OTf)_3$ [8], $AlCl_3$, $BF_3.Et_2O$ [9] SBA-15/SO_3H [10], TPPMS/CBr_4 [11], PEG-supported dichlorophosphate [12], $H_3PW_{12}O_{40}$ [13], Ionic Liquid [Et3NH] [HSO4] [14], $NaHSO_4.SiO_2$ [15] and $KHSO_4$-SiO_2 [16] has been used. Many of these methods have disadvantages such as long reaction times [17], use of expensive reagents or preformed reagents [18,19] and poor yield of products etc.

Solvent-free reaction condition has been demonstrated to be an efficient technique for various organic reactions. It often leads to remarkable decrease in reaction time, increased yields, easier workup, and enhanced regio- and stereo-selectivity of reaction [20,21]. In continuation of our work in bis(indolyl) methane synthesis [22,23] herein, we reports a green and efficient protocol for the synthesis of bis(indolyl) methane derivatives using mild and inexpensive $La(OTf_{)3}$ catalyst from indole and aromatic aldehydes under microwave irradiation in excellent yields (Scheme 1).

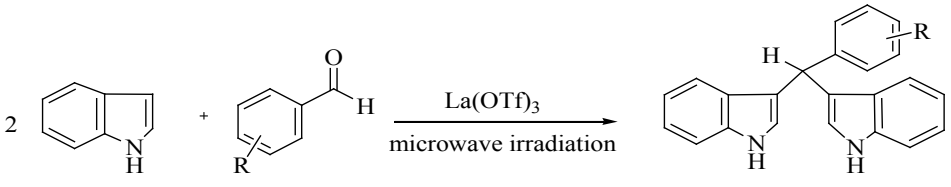
Experimental Procedure

Material and methods

All the reagents indoles and aromatic aldehydes were purchased from commercial suppliers and were not purified. Melting points were determined in open capillaries and are uncorrected. Completion of reactions was monitored on TLC. 1HNMR spectra were recorded on Varian NMR spectrometer Mercury Plus (400MHz) Model, Mass spectra [ES-MS] were recorded on Water-Micro mass Quattro-II spectrophotometer. For the microwave irradiation experiments described below, a scientific microwave oven was used (Essential Microwave Oven by Ragas Model No. 069 operating at 2450 MHz having maximum output of 900 W).

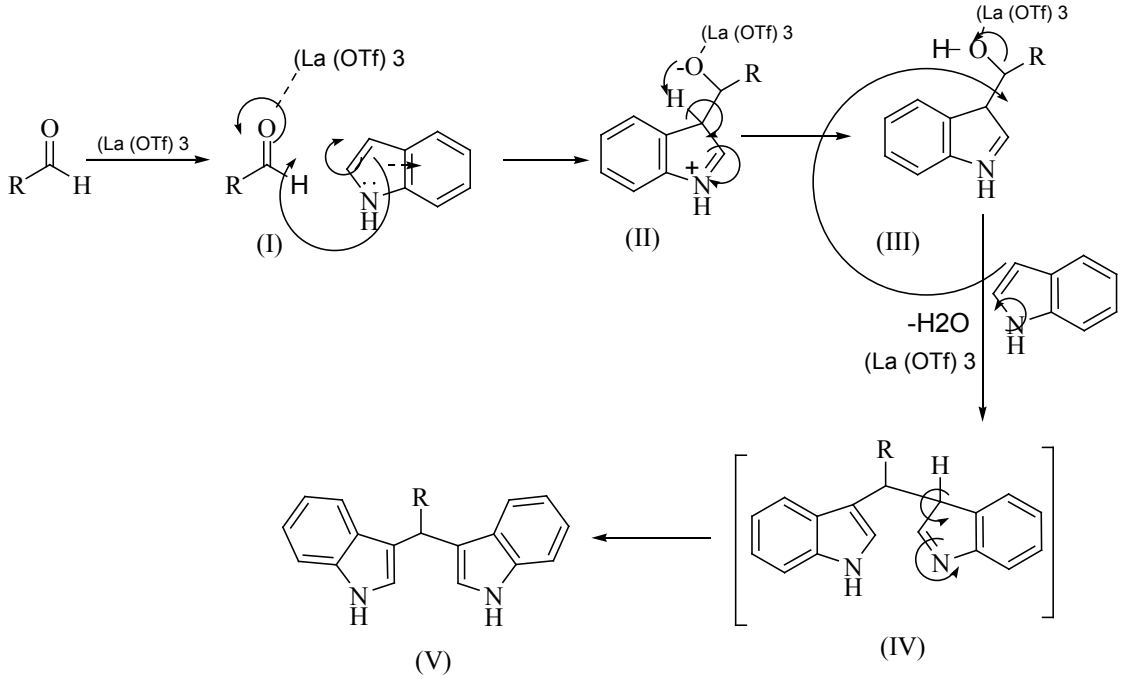
General procedure for the synthesis of bis(indolyl) methane using La$(OTf)_3$ as a catalyst

A mixture of (2.0 mmol) indole, (1.0 mmol) benzaldehyde and catalytic amount (10 mole %) $La(OTf)_3$ in beaker was irradiated at 450W under microwave oven for appropriate time. The completion of reaction was monitored by TLC. After completion of reaction the mixture was poured onto crushed ice to get desired crude product. The crude product was recrystallized by alcohol in high yield in short reaction time (Table 1).



1 2(a-p) 3(a-p)

Scheme 1. *Synthesis of bis(indolyl) methane.*



Scheme 2. *Plausible mechanism for the synthesis of Bis (indolyl) methane's.*

Table 1. *Characterization of Bis (indolyl) methane's (3a-3p).*

Product	R	Time (min.)	Yield[b] %	Melting Point (°C) Found	Reported
3a	H	3.0	92	203-204	202-204
3b	4-OH	3.0	90	231-232	232-233
3c	4-NO2	2.5	87	241-243	245-247
3d	4-OMe	3.0	88	260-261	254-256
3e	4-Br	3.0	91	251-253	251-252
3f	3-OMe-4-OH	2.0	91	205-209	202-204
3g	2-thienyl	2.5	90	151-153	152-154
3h	4-$(CH_3)_2$-N	3.0	88	176-178	178-181
3i	4-Cl	3.0	92	243-244	244-246
3j	4-F	3.0	87	183-185	184-185
3k	3,4-$(OMe)_2$	2.5	89	195-197	197-199
3l	4-Me	2.5	86	261-262	265-268
3m	2-Naphthaldehyde	2.0	88	102-103	--------
3n	Pyridyl-2-carbaldehyde	3.0	87	137-139	136-138
3o	Cinnamaldehyde	2.5	89	99-100	98-99
3p	Pyrol-2-carbaldehyde	3.0	88	≥ 3000	.....

[a]Reaction conditions: indole (2 mmol), benzaldehyde (1 mmol), La(OTf)$_3$ (10 mol%) under microwave irradiation at 450 W and 120 ºC. [b]Isolated yield

Similarly, the other derivatives were also prepared using same procedure and further were confirmed by comparing M.Ps. and other authentic spectral data.

Spectral data of selected compounds

3-((1H-indol-3-yl) (thiophen-2-yl) methyl)-1H-indole (3g):

1H NMR [300 MHz,$CDCl_3$]:δ 5.97 (s, 1H, CH), 6.82-6.83 (s, 2H), 6.85-6.87 (d,1H, j=6.0 Hz), 6.88-6.89 (d,1H, j=3.3), 6.90-6.91 (d,1H, j=3), 7.02-7.35 (m, 8H, Ar), 7.36 (s,br,2H,NH) 13C NMR (MeOH, 75.46MHz) δ 48.87, 112.34, 119.98, 120.49, 122.40, 124.52, 125.91, 126.03, 127.26, 128.26, 138.52, 150.02, 151.16. EI-MS (%): m/z=328.30 (M+1)

3-((1H-indol-3-yl) (naphthalen-3-yl) methyl)-1H-indole (3m)

1H NMR [300 MHz,$CDCl_3$]:δ 5.99 (s,1H,CH),6.60-6.61 (s,2H),6.9-7.75(m,15H,Ar), 8.28 (s,br,2H,NH) 13C NMR (MeOH, 75.46MHz)δ,52.33,111.01,111.46, 119.30, 119.36, 1119.94, 121.96, 124.01, 125.46, 125.90, 126.24, 126.78, 127.01, 127.23, 127.88, 127.91, 128.03, 132.46, 133.74, 136.86, 142.07 EI-MS (%):m/z=372.36 (M+1)

3-((1H-indol-3-yl) (pyridin-2-yl) methyl)-1H-indole (3n)

1H NMR [300 MHz, $CDCl_3$]: δ 6.00 (s,1H,CH), 6.7 2 (s,2H), 7.19-7.7 2 (m,4H,Ar), 6.87-7.08 (m,8H,Ar), 8.40-8.47 (s,br,2H,NH) 13C NMR (MeOH, 75.46MHz): δ 50.00, 112.42, 118.32, 119.79, 120.25, 122.56, 123.08, 124.97, 128.40, 138.67, 149.29, 165.61 EI-MS(%): m/z=323.90 (M+1)

3-((E)-1-(1H-indol-3-yl)-3-phenylallyl)-1H-indole (3o)

1H NMR [300 MHz,$CDCl_3$] : δ 4.82 (s,1H,CH) 6.76 (s,1H), 6.78 (s,1H,ethylen), 6.81 (s,1H,ethylene) 6.83-6.88 (s,2H), 6.93-7.37 (m,13H,Ar), 7.38 (s,br,2H,NH) 13C NMR (MeOH, 75.46MHz) δ 53.24, 112.27, 112.33, 112.40, 119.35, 119.43, 119.53, 119.66, 120.11, 120.28, 120.37, 120.61, 120.69, 121.07, 121.24, 122.20, 122.29, 122.37, 122.79, 123.20, 127.04, 128.35, 128.41, 128.55, 129.15, 129.32, 129.54, 129.95, 138.44, 138.56, 147.33 EI-MS(%): m/z=350.21 (M+1)

3-((1H-indol-3-yl) (1H-pyrrol-2-yl) methyl)-1H-indole (3p)

1H NMR [300 MHz,$CDCl_3$]: δ 6.41 (s,1H,cH), 4.8 3 (s,1H,NH), 6.42-6.77 (s,2H), 6.95-6.97 (m,3H), 6.98-7.53 (m,8H,Ar),7.54 (s,br,2H,NH) 13C NMR (MeOH, 75.46MHz) δ 53.38,102.37 ,112.23,112.84,119.34,119.45,120.09,120.36,120.74,121.27,12 2.11,122.29,123.54,124.63,125.57,128.71,129.46,129.57,137.7 9 EI-MS(%): m/z=311.14 (M+1)

Results and Discussion

In continuation of our research and interest in the development of novel synthetic methodologies herein, we would like to report $La(OTf)_3$ as an efficient catalyst for the formation of bis(indolyl) methanes by one-pot two component reaction of an indole and aldehyde under solvent-free conditions The electrophilic substitution reaction of indole with aldehydes in presence of $La(OTf)_3$ under microwave irradiation afforded the corresponding bis-(indolyl) methane derivatives within few minutes (Scheme 2). The experimental procedure for these reactions is ease to handle and does not require an inert atmosphere. This method responds well for a wide variety of aromatic aldehydes (Table 1). Electron withdrawing group in aromatic ring increases the yield of the reaction (Table 1 entries 3g) and the electron donating group decreases the rate of reaction.

The reactions were carried out under solvent free conditions; therefore the use of hazardous solvents has been avoided. In order to explore the best reaction conditions, a mixture of (2.0 mmol) indole, (1.0 mmol) benzaldehyde with catalytic amount of $La(OTf)_3$ (10 mole %) in a beaker was irradiated at 450W in microwave oven for appropriate time. Completion of the reaction was confirmed on TLC. The crude product was poured onto crushed ice and filtered; washed with water and recrystallized by alcohol. To determine the required concentration of catalyst for this reaction; the model reaction is carried out using various concentrations of catalyst (Table 2). 10 mole % of catalyst was found to be more effective for the formation of product in high yield in short time period of 3 minutes (Table 2).

To check the catalytic utility of $La(OTf)_3$, we carried out model reaction using several catalysts (Table 3). Among them, $La(OTf)_3$ was found to be more efficient for this transformation. In presence of $La(OTf)_3$ the reaction goes smooth and clean due to its higher solubility in aqueous medium. In rest of the catalyst presence (10 mole %), the reaction required very high time period and the yield of products were also found to be less as compare to catalyst $La(OTf)_3$.

***Table 2**. Screening of catalyst concentration on model reaction[a].*

Entry	Catalyst	Catalyst (mol%)	Time (min)	Yield[b] (%)
1	$La(OTf)_3$	4	32	70
2	$La(OTf)_3$	6	25	79
3	$La(OTf)_3$	8	15	83
4	$La(OTf)_3$	10	03	92
5	$La(OTf)_3$	12	03	92

[a]Reaction conditions: indole (2 mmol), benzaldehyde (1 mmol) under microwave irradiation at 450 W and 120 ºC. [b]Isolated yield

***Table 3.** Optimization of catalyst in model reaction[a].*

Entry	Catalyst	Catalyst Conc. (mol %)	Time (min)	Yield[b] (%)
1	$Sc(OTf)_3$	10	30	70
2	$Yb(OTf)_3$	10	25	74
3	$Sm(OTf)_3$	10	25	79
4	$Ga(OTf)_3$	10	20	80
5	$La(OTf)_3$	10	03	92

[a]Reaction conditions: Indole (2 mmol), benzaldehyde (1 mmol) under microwave irradiation at 450 W and 120 ºC. [b]Isolated yield

Conclusion

In conclusion this present protocol affords bis(indolyl) methanes in excellent yields employing mild, efficient, catalyst $La(OTf)_3$. This new protocol has silent features like cleaner reaction, simple experimental and easy work-up procedures, high conversions, shorter reaction time to afford the products in excellent yield, hence believed to be superior over many existing synthetic methods of catalysts.

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