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Synthesis of bis(indolyl)methanes using La(OTf)3 as an efficient catalyst under solvent-Free condition

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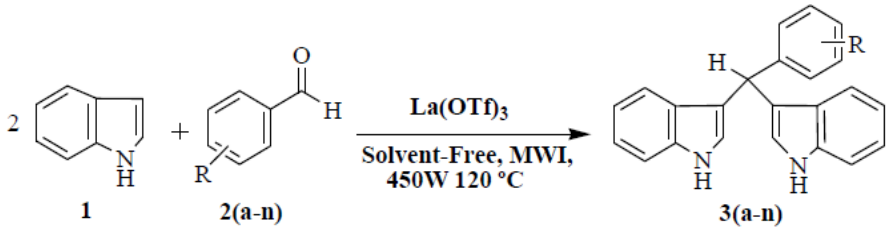
Abstract-

In this present protocol affords bis(indolyl)methanes in excellent yields employing mild, efficient, catalyst La(OTf)$_3$. Reaction of benzaldehyde and indole was considered as amodel reaction. The reaction mixture was irradiated at 120 ºC and 450 W in microwave oven for appropriate time to give desired products 3a-n.All the products were further confirmed by spectral analysis.0



Scheme I Synthesis of bis(indolyl)methane.

Keywords bis indolyl methane, La(OTf)$_3$, substituted benzaldehyde, MWI.

I. INTRODUCTION

Indole and their derivatives constitute an important class of biologically active natural products, which play a fundamental role in medicinal chemistry.[1]Indole itself has been obtained, usually in small amounts, by extraction from naturally occurring materials. Various plants have yielded indole, among them the following: Robinia pseudacacia[2] the jasmines [3-5] certain citrus plants[7] and orange blossoms.[6] Indole is also found after putrefactive processes has takes place. It is foundin the animal body wherever pus formation occurs[8] in the liver pancreas[9] the brain[10] and bile.[11]

Indole and its derivatives are important intermediates in organic synthesis and exhibit various physiological properties and pharmacological activities, such asbeneficial estrogen metabolism promoter[12] inhibitory of human prostate cancer cells[13] and radical scavenging activities associated with cancer cells.[14]In recent years a large trend towards synthesis of bis(indolyl)methanes and their derivatives has attracted much attention due to their synthetic as well as biological applications.[15] The most ubiquitous of the known bioactive alkaloids are based on the indole moiety.[16] Because of their wide occurrence as natural products and various biological activities, synthesis of these bis(indolyl)methane have attracted attention. Recently bis(indolyl)methane containing a conjugated bis(indolyl) skeleton have acted as colorimetric sensors and chromogenic sensors.[17]

In present work, we developed a simple and efficient procedure for the synthesis of bis(indolyl)methane in presence of La(OTf)$_3$ as catalysts under solvent free condition using microwave irradiation at 450W and 120 ºC.

I. EXPERIMENTAL SECTION

All the reagents were obtained from commercial suppliers and were not purified. Melting points were determined in open capillaries and are uncorrected. The completion of reactions was monitored by TLC. 1H NMR and 13C NMR spectra were determined in DMSO-d6 or MeOD on a BRUKER DRX-300 AVANCE spectrometer at 300.00 and 75.47 MHz, respectively Mass spectra [ES-MS] were recorded on a Water-Micro mass Quattro-II spectrophotometer.

General Procedure for the synthesis of bis(indolyl) methane using La(OTf)3 3(a-m)

Benzaldehyde (1.0 mmol) and (2.0 mmol) indole was mixed with a catalytic amount of La(OTf)3 (10%) in RB flask. The reaction mixture was irradiated at 120 ºC and 450 W in microwave oven for appropriate time. The progress of reaction monitored by TLC (ethyl acetate: hexane, 3:7). After completion of the reaction resultant product poured on crushed ice and filtered the solid product. The products were recrystallized from alcohol.

Spectral Data

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

^{1}H NMR [300 MHz, MeOH]: δ 5.99 (s, 1H, CH), 6.60-6.61 (s, 2H Ar), 6.9-7.75 (m, 15H, Ar), 8.28 (s, br, 2H, NH)

^{13}C NMR (MeOH, 75.46 MHz) δ: 52.3, 111.0, 111.4, 119.3, 119.4, 120, 122, 124.0, 125.5, 125.9, 126.24, 126.8, 127.0, 127.2, 127.9, 127.9, 129.0, 132.5, 133.5, 136.7, 142.0. **EI-MS** m/z cal 372.16 m/z obs.($M+H)^{+\cdot}$ 372.36.

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

^{1} H NMR [300 MHz,CDCl3]: δ 6.00 (s,1H,CH), 6.72 (s,2H), 7.19-7.72 (m,4H,Ar), 6.87-7.08 (m,8H,Ar), 8.40-8.47 (s,br,2H,NH) **$^{1\,3}$C NMR (75.46 MHz, MeOD) δ** 50.0, 112.4, 118.3, 119.8, 120.2, 122.6, 123.1, 125, 128.4, 138.6, 149.3, 165.6. **EI-MS** m/z cal 323.14 m/z obs. $(M + H)^{+\cdot}$ 323.90.

II. RESULTS AND DISCUSSION

For the reaction of benzaldehyde and indole was considered as a model reaction. Firstly we carried out model reaction in the absence of catalyst that did not led to the formation of desired product after long time. It means intervention of catalyst is necessary for initiation of the reaction. After screening of catalyst we tested the optimum concentration of $La(OTf)_3$ catalyst for model reaction by using different concentration of La(OTf)3 such as 4, 6, 8, and 10 mol% . They reveal that 10 mol% of Lanthanide trifluromethane sulfonates was sufficient to give product in excellent yield and short time. Further increasing the concentration of catalyst, reaction did not showed. Improvement in yield of product. Also we compare the result of ultrasound irradiation as well as conventional method, which showed that microwave irradiation technique was superior in terms of reaction times and yield of products. **(Table 1, 2, 3)**

Table 1. Screening of Catalyst on model reaction[a]

Entry	Catalyst	Catalyst Conc. (mol%)	Time (min)	Yield[b] (%)
1	$Sc(OTf)_3$	8	30	70
2	$Yb(OTf)_3$	8	25	74
3	$Sm(OTf)_3$	8	25	79
4	$Ga(OTf)_3$	8	20	80
5	**$La(OTf)_3$**	**8**	**10**	**83**

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

Table 2. Screening of Catalyst on model reaction[a]

Entry	Catalyst	Catalyst Conc. (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**	**95**
5	$La(OTf)_3$	12	03	95

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

Table 3.Reaction time, yield and Melting points of 3a-3n

Product	R	Time (min)	Yield[b] %	Melting Point (°C)
3a	H	03	92	203-204
3b	4-OH	03	90	231-232
3c	4-NO2	2.5	87	241-243
3d	4-OMe	3	88	260-261
3e	4-Br	3	91	251-253
3f	3-OMe-4-OH	2	91	205-209
3g	2-thienyl	2.5	90	151-153
3h	$4-(CH_3)_2-N$	3	88	176-178
3i	4-Cl	3	92	243-244
3j	4-F	3	87	183-185
3k	$3,4-(OMe)_2$	2.5	89	195-197
3l	4-Me	2.5	86	261-262
3m	2-Napthaldehyde	2	88	102-103
3n	3-pyridyl	3	87	137-139

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

VI. CONCLUSION

In 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 times to afford the products in excellent yield, hence believed to be superior over many existing synthetic methods of catalysts.

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