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# Synthesis of bis(indolyl)methanes catalyzed by ceric ammonium nitrate (CAN) under solvent free conditions

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## ABSTRACT

The ceric ammonium nitrate (CAN) was found to efficiently catalyze the one-pot synthesis of bis (indolyl)methanes by the reaction of indole with aldehydes under a solvent-free condition. Various aliphatic and aromatic aldehydes or ketones were utilized in the reaction and in all situations the desired product were synthesized successfully. The described novel synthesis method offers several advantages such as safety, mild condition, short reaction times, high yields, simplicity and solvent-free condition compared to the traditional method of synthesis.



## KEYWORDS

Bis(indolyl)methan;
Ceric ammonium nitrate (CAN);
Indole;
Solvent free;
One pot synthesis.

## INTRODUCTION

In recent years, indole and their derivatives are known as important intermediates in organic synthesis and pharmaceutical chemistry and exhibit various physiological properties[1]. Bis(indolyl) methanes are a biologically valuable group of organic compounds. A large number of these compounds have been isolated from earthly and marine natural sources such as sponges[2]. Among them, bis(indolyl)methanes are the most cruciferous substances for promoting beneficial estrogen metabolism in men and women[3]. They are also effective in the prevention of cancer due to their ability to modulate certain cancer causing estrogen metabolites[4]. Moreover, these compounds may normalize abnormal cell growth associated with cervical dysplasia[5]. The condensation of indoles with carbonyl compounds has been used as an useful route toward bis(indolyl)methanes synthesis. Different reagents and catalysts have been applied to achieve this transformation, including $AlPW_{12}O_{40}$[6], $ZrOCl_2.8H_2O$[7], $In(OTf)_3$[8], $Ln(OTf)_3$[9], Zeokarb-225[10], $LiClO_4$[11], $La(PFO)_3$[12], $Dy(OTf)_3$[13], surfactant[14,15], CAN[16], $PPh_3.HClO_4$[17], $ZrCl_4$[18], trichloro-1,3,5-triazine[19], aminosulfonic acid[20], HY-Zeolite[21], silica sulfuric acid[22], silica chloride[23], and $P_2O_5/SiO_2$[24]. However, most of the existing methods involve toxic metal ions and solvents, have high costs and use corrosive reagents. A mild and efficient catalyst for the synthesis of bis(indolyl)methanes is very desirable.

## RESULTS AND DISCUSSION

In continuation with the search for simple non-hazardous methods for the transformations in organic

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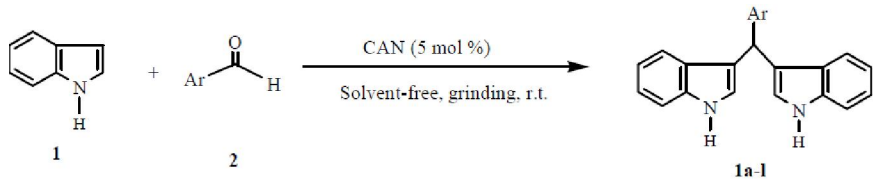
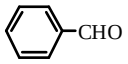
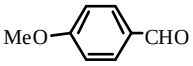
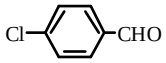
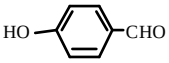
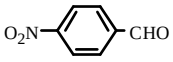
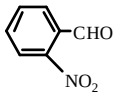
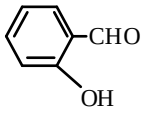
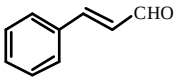
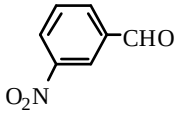
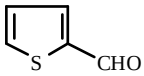
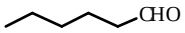



**Scheme 1 : Synthesis of Bis(indolyl)methanes by Ceric Ammonium Nitrate (CAN)**

**TABLE 1 : Synthesis of bis(indolyl)methanes by the reaction of indole with aldehydes and ketones**

| Entry | Substrate | Product | Time(min) | Yelde(%) | M.P(°c) |
|---|---|---|---|---|---|
| 1 |  | 3a | 5 | 96 | 126-128 |
| 2 |  | 3b | 8 | 90 | 190-192 |
| 3 |  | 3c | 6 | 96 | 104-106 |
| 4 |  | 3d | 10 | 88 | 122-124 |
| 5 |  | 3e | 5 | 96 | 225-227 |
| 6 |  | 3f | 8 | 94 | 144-146 |
| 7 |  | 3g | 10 | 88 | 122-124 |
| 8 |  | 3h | 7 | 94 | 98-100 |
| 9 |  | 3i | 6 | 97 | 220-222 |
| 10 |  | 3j | 8 | 88 | 149-150 |
| 11 |  | 3k | 15 | 82 | 70-72 |

**a) All the products are known, characterized by IR, NMR spectral analysis and compared with the authentic samples; b) Isolated yields. c) Melting points of compounds are consistent with reported values[9, 13, 20].**

synthesis using various reagents[25-32], we wish, herein, to report on the use of CAN as a more robust and efficient catalyst in the one-pot synthesis of bis(indolyl)methanes (3a-k) from condensation of various aldehydes (2a-k) with indole (1) under a solvent-free condition.

At first, we studied the reaction of indole with benzaldehyde (2/1 molar ratio) in order to optimize the reaction conditions with respect to temperature and molar ratio of CAN to the substrate. We found that 5 mol % of CAN was sufficient to produce the desired bis(indolyl)methane 1a in 96% yield within 5 min in solvent free at room temperature Scheme 1.

After optimizing these conditions using benzaldehyde as a model aldehyde, the reactions were performed with various other aryl aldehydes, and it was noticed that the reaction proceeds well with all types of aryl aldehydes and the results of this study are presented in TABLE 1.

## EXPERIMENTAL

Chemicals were obtained from Merck and Fluka chemical companies. The IR spectra were recorded on a Shimadzu 435-U-04 spectrophotometer (KBr pellets) and NMR spectra were obtained in $CDCl_3$

using a 400 MHz JEOL FT NMR spectrometer. All melting points were determined on an Electro Thermal 9100 melting point apparatus.

## GENERAL PROCEDURE FOR THE SYNTHESIS OF BIS(INDOLYL)METHANES IN SOLID-STATE CATALYZED BY CAN

A mixture of indole (2.0 mmol), aldehyde or ketone (1.0 mmol) and CAN (5 mol %) were added to a mortar and the mixture was pulverized with a pestle. A spontaneous reaction took place [5-15 min, TABLE 1, monitored by TLC (4:1, hexane/ acetone)]. After completion of the reaction, $CH_2Cl_2$ (10 mL) was added, and insoluble reagents were removed by filtration. The filtrate was evaporated under reduced pressure and the resulting crude material was purified by recrystallization from ethanol-water to afford pure products.

## CONCLUSION

In conclusion, a new strategy has been developed for the convenient synthesis of bis(indolyl)methane derivatives using CAN as a highly efficient catalyst. In the presence of this solid acid a series of tandem condensation and dehydration reactions occurred and resulted in the formation of bis(indolyl)methane derivatives in high yields. The advantages of this work are solvent-free conditions and recyclability of catalyst. The simplicity of the present procedure than the previously reported method of bis(indolyl)methanes synthesis makes this new approach as an interesting alternative to the complex multi step approaches.

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