



Synthesis of bis (indolyl) methanes catalyzed by molybdate sulfuric acid (MSA)

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ABSTRACT

The molybdate sulfuric acid (MSA) 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.

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KEYWORDS

Bis (indolyl) methan;
 Molybdate sulfuric acid
 (MSA);
 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 crucial 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

AIPW12O40^[6], ZrOCl₂.8H₂O^[7], In(OTf)₃^[8], Ln(OTf)₃^[9], Zeokarb-225^[10], LiClO₄^[11], La(PFO)₃^[12], Dy(OTf)₃^[13], surfactant^[14,15], CAN^[16], PPh₃.HClO₄^[17], ZrCl₄^[18], trichloro-1,3,5-triazine^[19], aminosulfonic acid^[20], HY-Zeolite^[21], silica sulfuric acid^[22], silica chloride^[23], and P₂O₅/SiO₂^[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

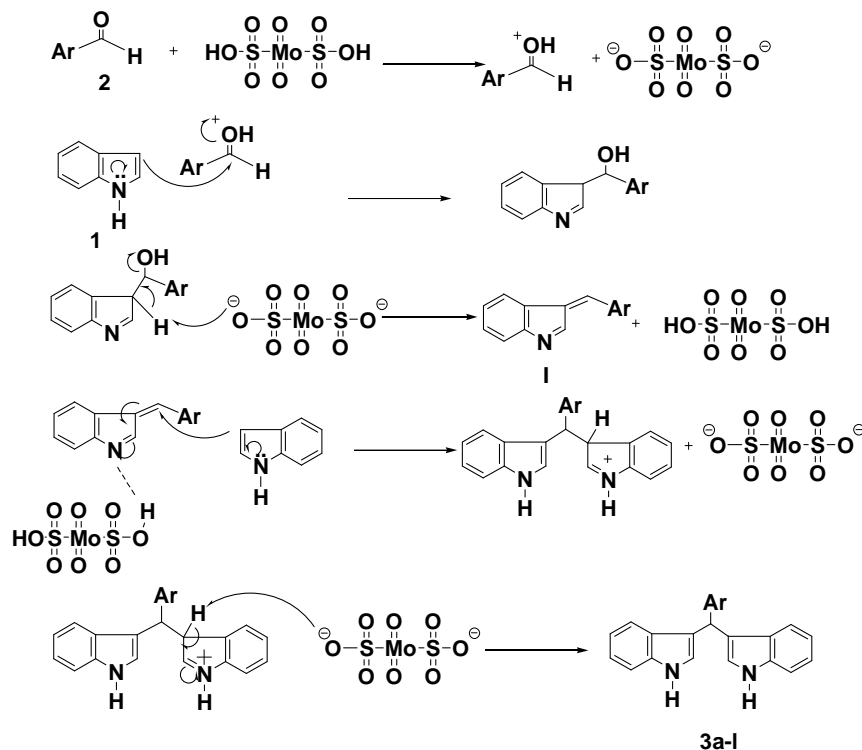
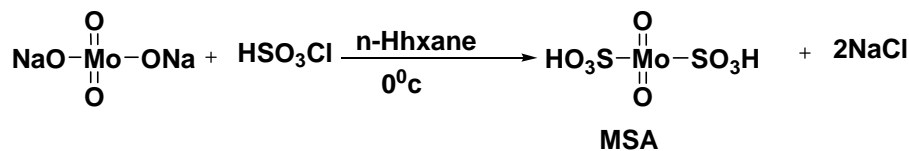
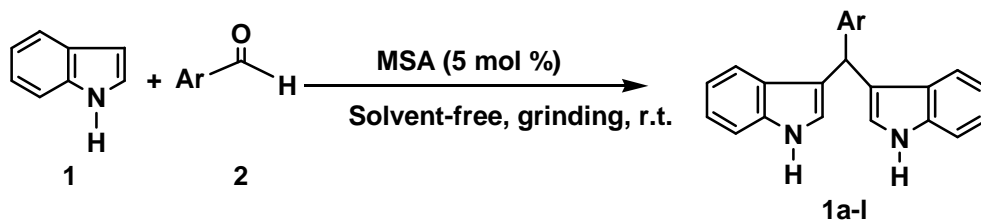
In continuation with the search for simple non-hazardous methods for the transformations in organic synthesis using various reagents^[25-32], we wish, herein, to report on the use of MSA as a more robust and efficient catalyst in the one-pot synthesis of bis(indolyl)methanes (**3a-k**) from condensation of various aldehydes (**2**) with indole (**1**) under a solvent-free condition.

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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 MSA to the substrate. We found that 5 mol % of MSA was sufficient to produce the desired bis(indolyl)methane (**1a**) in 96% yield within 5 min in solvent free at room temperature (Scheme 1).

Molybdate sulfuric acid is an easily prepared and moisture tolerant solid acid which has been used as catalyst in the oxidation of thiols and nitrosation of amines^[33,34]. The reusability of catalyst is an important factor for commercial uses. Therefore, the recovery and

reusability of MSA was investigated. Hence, MSA was successfully regenerated from the model reaction by washing with EtOAc and drying at 120 °C. Attempts to the reusability of MSA showed that reactivity of the recovered catalyst was efficiently depending on the solvent applied for regeneration of catalyst. However, washing the filtered catalyst from the first run by warm protic solvents such as water and alcohols resulted in the obvious decreasing of reaction yield. In the contrast, the recycled catalyst by EtOAc was reused three times with gradual loss of activity in the model reaction. (Scheme 2)



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.

We propose a mechanism for these reactions in five steps as shown in Scheme 3. Thus, the aldehydes act as *Michael* acceptors and the indole as the nucleophiles resulting in a *Michael* adduct which, under the influence of MSA, forms an intermediate (**I**) which undergoes nucleophilic reactions with indole to afford bis(indolyl)methane derivatives. The advantages or the characteristic aspects of the method described herein, in comparison with those already reported are the following: The yields of products are better than the pre-

viously reported yields. In addition, the catalyst MSA is inexpensive and not moisture sensitive and only sub-molar amounts of MSA are required. Longer reaction times are required when smaller amounts of MSA are employed. It is important to note that no bis(indolyl)methane derivatives were formed when the reactions were carried out in the absence of MSA.

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 CDCl₃ using a 400 MHz JEOL FT NMR spectrometer. All melting points were determined on an Electro Thermal 9100 melting point apparatus.

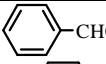
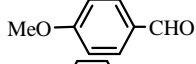
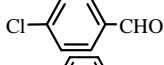
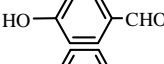
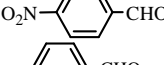
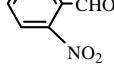
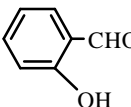
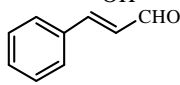
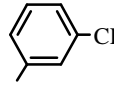
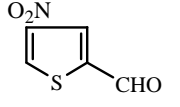
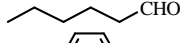

Preparation of catalyst

MSA was prepared via a modified version of the previously reported procedures^[2,3] (Scheme 2). Thus, anhydrous sodium molybdate (20 mmol, 4.118 g) was added to dry n-hexane (25 mL) in a 100 mL round bottom flask equipped with ice bath and overhead stirrer. Chlorosulfonic acid (0.266 mL, 40 mmol) was then added dropwise to the flask during 30 min and stirred for 1.5 h. The reaction mixture was gradually poured into 25 mL of chilled distilled water with agitation. The molybdate sulfuric acid was separated as a bluish solid by filtration, washed with cold distilled water five times until the negative test for chloride ion for filtrate, and dried at 120 °C for 5 h. The yield of the obtained bluish acid catalyst was 90%.

Characterization of catalyst

The prepared catalyst was characterized by determination of decomposition point, FT-IR spectrum, and neutralization titration with standard solution of NaOH. As a result, the prepared molybdate sulfuric acid which showed good thermal stability decomposed at 354 °C. The overlaid FT-IR spectra of sodium molybdate and molybdate sulfuric acid (MSA) are shown in Figure 1. As the spectrum of MSA demonstrates, the characteristic bands of both anhydrous sodium molybdate and -OSO₃ group are shifted evidently to the higher wave numbers. The well defined bands at 3600–3000 is re-

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

Entry	Substrate	Product	Time (min)	Yield (%)	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
12		3l			93-95

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].

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lated to OH stretching, the band at 1635 cm^{-1} is the H-O-H bending mode of the lattice water, and the bands at $1300\text{--}1100\text{ cm}^{-1}$ might be the asymmetric and symmetric stretching modes of S=O. A strong band at 827 cm^{-1} in the FT-IR spectrum of sodium molybdate is assigned to the stretching mode of Mo-O. This band is shifted to $\sim 1100\text{ cm}^{-1}$ and appeared as an overlapped band with S=O stretching bands in spectrum of MSA. Broadening of the absorbance band positioned at $3600\text{--}3000\text{ cm}^{-1}$ is due to the rapid exchanges of acidic hydrogens via H-bonding and reveals the formation of MSA. In order to investigate the acid capacity of MSA, a solution of it (0.0805 g) in distilled water (100 mL) was titrated with standard solution of NaOH (0.1 N) in the presence of phenolphthalein as indicator. At the endpoint of titration 5 mL of titrant was consumed. The capacity of MSA was determined according the following equation as $2 \cdot (m/MW) \times n = N_2V_2$, $(0.0805/322) \times n = 0.1 \times 0.005$, thus $n = 2$. Therefore, MSA can be considered as a solid heterogeneous alternative to sulfuric acid.

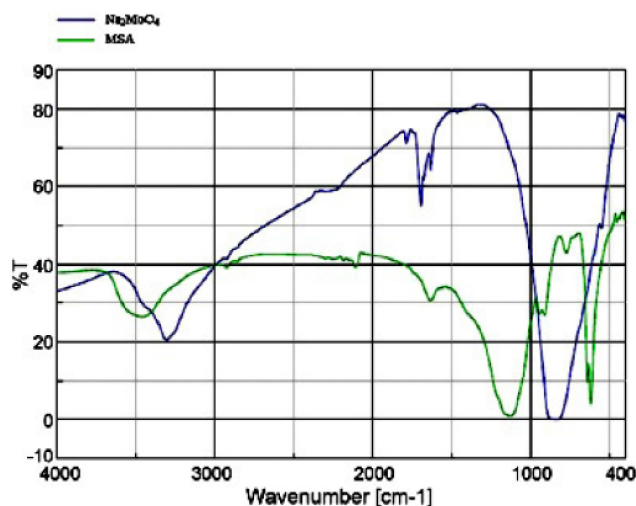


Figure 1 : Overlaid FT-IR spectra of Na_2MoO_4 and $\text{H}_3\text{OSO}(\text{MoO}_2)\text{OSO}_3\text{H}$ (MSA).

General procedure for the synthesis of bis(indolyl)methanes in solid-state catalyzed by MSA

A mixture of indole (2.0 mmol), aldehyde or ketone (1.0 mmol) and MSA (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 MSA 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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