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Application of Natural Kaolin Supported Sulfuric Acid as an Ecofriendly Catalyst for the Efficient Synthesis of bis(indolyl)methanes

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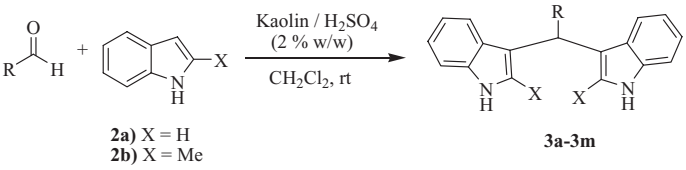
The acidified kaolin with sulfuric acid (2% w/w) is introduced as a novel, mild, highly efficient, easily prepared, very cheap, recyclable and ecofriendly catalyst in organic synthesis. This catalyst has been used successfully for the synthesis of *bis*(indolyl)methanes *via* the condensation of indoles with aldehydes at room temperature. The simplicity, efficiency, mild reaction condition, high yield of product, easy work up procedure, and recyclability of the catalyst are the advantages of this procedure.

Keywords kaolin, heterogeneous catalyst, bis(Indolyl)methanes, Indoles, aldehydes

INTRODUCTION

Indole derivatives are present in many substances commonly found in nature,[1, 2] as well as in many compounds with pharmacological and biological activities.[3–5] Bis(Indolyl)methane derivatives are very important compounds as they display various biological and pharmaceutical activities.[6, 7] Therefore, a number of synthetic methods for preparation of bis(indolyl)alkane derivatives has been reported in the literature by reaction of indole with various aldehydes and ketones in the presence of protic acid,[8] Lewis acid,[9, 10] heterogeneous acidic catalysts,[11, 12] and reagents such as I_2,[13] NBS,[14] CAN,[15] ionic liquids,[16–19] and heteropolyacid.[20] However, there are still some drawbacks to these catalytic systems, including the requirement for large amounts of catalyst, long reaction times, low yield of product, tedious workup leading to the generation of large amount of toxic waste, highly expensive catalysts and drastic reaction conditions for catalyst preparation. For these reasons, a superior catalyst which is cheap, less toxic, and easily available and air stable is desirable. However, to the best of our knowledge, there is no report on the use of kaolin as a catalyst for this conversion. In this paper we will report natural kaolin as an efficient, mild, inexpensive and recyclable catalyst for the preparation of bis(indolyl)methanes through condensation of aldehydes with indoles (Scheme 1).



SCH. 1.

EXPERIMENTAL

All materials and solvents were purchased from Merck and Fluka. Melting points were determined in open capillary tubes in an Electrothermal IA 9700 melting point apparatus. ^{1}H-NMR spectra were recorded on a Bruker-100 MHz and 500 MHz instruments using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a Shimadzu-IR 470 spectrophotometer.

Preparation of the Acidified Kaolin with Sulfuric Acid (2% w/w)

20 mL n-Hexane and (0.15 g, 0.08 mL) concentrated sulfuric acid were added to natural kaolin (7.5 g) in a round bottomed flask respectively and stirred for 1h. Then the mixture was filtered and dried. The prepared acidified kaolin (2% w/w), was stored for further applications.

General Procedure for the Synthesis of bis(Indolyl) methanes

To a solution of indole (2 mmol) and aldehyde (1 mmol) in dichloromethane (5 mL), the acidified kaolin (2% w/w) (75 mg), was added and stirred vigorously at room temperature until the disappearance of the starting materials (15–35 minutes). After completion of the reaction as monitored by TLC, the precipitate was filtered and washed with cold mixture of *n*-hexane-dichloromethane (1:1, 4 mL). The product was washed from

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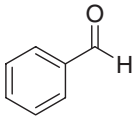
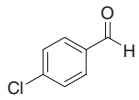
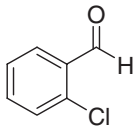
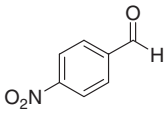
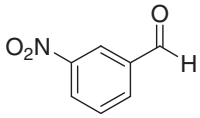
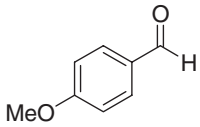
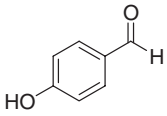
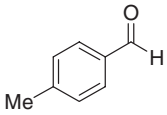
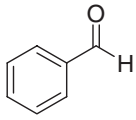
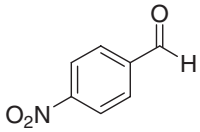
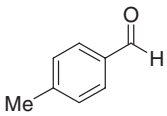
TABLE 1
Synthesis of bis(indolyl)methanes in the presence of kaolin / sulfuric acid (2% w/w).

Entry	Aldehyde	X	Product[a]	Time (min.)	Yield (%)[b]	Mp/°C Found	Mp/°C Reported [lit.]
1		H	**3a**	25	92	140–141	140–142 [25]
2		H	**3b**	20	90	77–78	78–80 [26]
3		H	**3c**	20	85	74–75	74–76 [19]
4		H	**3d**	20	88	217–218	217–219 [19]
5		H	**3e**	20	90	219–220	218–220 [25]
6		H	**3f**	25	93	185–186	186–188 [18]
7		H	**3g**	20	80	120–121	119–120 [26]
8		H	**3h**	25	91	97–98	97–99 [27]
9	CH_3-$(CH_2)_4$-CHO	H	**3i**	25	91	71–72	71–73 [25]
10	CH_3-$(CH_2)_5$-CHO	H	**3j**	35	69	65–66	66–68 [19]
11		Me	**3k**	20	95	245–246	247–248 [21]
12		Me	**3l**	15	92	240–241	240–242 [28]
13		Me	**3m**	20	90	176–177	174–177 [25]

[a]The products were characterized by IR and ^{1}H-NMR spectroscopy and also their melting points are compared with authentic samples.
[b]Isolated yields.

catalyst with ethyl acetate (3 × 10 mL). The organic extracts were combined and washed with saturated solution of $NaHCO_3$ (2 × 15 mL) and then with water (15 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by recrystallization from suitable solvent such as ethanol-water. The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by the procedure given in the references.

RESULTS AND DISCUSSION

Natural kaolin is very cheap and shows good potential as support material. Currently, strong interests in such natural supports are due to ecofriendly demands in many modern industrial applications.[22–24] In this study, 2-methylindole (**2b**) was reacted with benzaldehyde in the presence of kaolin in dichloromethane and the reaction was completed after 4 hours at room temperature. But in the presence of acidified kaolin with sulfuric acid (2% w/w) the reaction was completed after 20 minutes and the product was obtained with excellent yield at room temperature.

In order to evaluate the applicability and scope of the catalyst, indole (**2a**) and 2-methylindole (**2b**) were treated with structurally diverse aldehydes (**1**) in the presence of acidified kaolin with sulfuric acid (2% w/w) in dichloromethane at room temperature. The results are shown in Table 1. As shown in Table 1, the catalytic electrophilic substitution reaction of substituted indoles proceeds with different benzaldehyde derivatives. Substituted benzaldehydes with electron-donating and electron-withdrawing groups underwent electrophilic substitution reaction with indole and 2-methylindole, and gave the corresponding bis(indolyl)methanes in 80–95% yields in short reaction times. Moreover, aliphatic aldehydes also react satisfactorily under this condition (Table 1, entries 9 and 10).

The products were characterized by IR and ^{1}H-NMR spectroscopy and also their melting points are compared with authentic samples. The disappearance of one strong and sharp absorption band of aldehydes carbonyl group in the IR spectra, and appearance of methine hydrogen of product at 5.8–6.1 ppm in the ^{1}H-NMR spectra confirm the bis(indolyl)methanes formation.

The recyclability of the catalyst was studied in the reaction of 2-methylindole with benzaldehyde. After performing the preparation reaction of bis(indolyl)methane (**3k**) under the conditions described in Table 1, the reaction mixture was washed with ethyl acetate. The separated catalyst was found to be reusable five times without significant loss of activity.

CONCLUSION

In conclusion, we have introduced the acidified kaolin with sulfuric acid (2% w/w), as a novel, mild, highly efficient, easily prepared, very cheap, recyclable and ecofriendly catalyst in organic synthesis. In this work, this catalyst has been used successfully for the synthesis of *bis*(indolyl)methanes *via* the condensation of indoles with aldehydes at room temperature. The simplicity, efficiency, mild reaction condition, high yield of product, easy work up procedure, and recyclability of the catalyst make it the preferred procedure for the preparation of *bis*(indolyl)methanes.

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