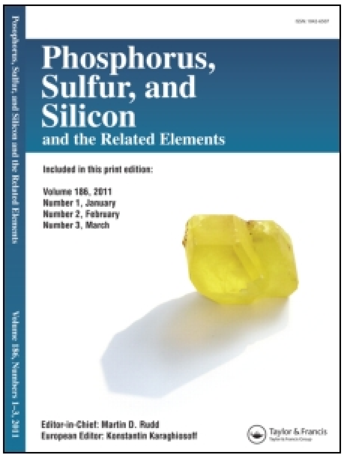

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AN EFFICIENT PROCEDURE FOR THE PREPARATION OF MONO, AND DI-BIS-INDOLYL METHANES CATALYZED BY MOLIBDATOPHOSPHORIC ACID

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$H_3PMo_{12}O_{40} \cdot xH_2O$ was found to be an effective catalyst for the preparation of bis-indolyl derivatives from indole and aromatic, aliphatic, heterocyclic aldehydes or ketones in ethanol at room temperature.

Keywords: Aldehyde; bis-indolyl methanes; heteropolyacids; indole; ketone

Acids are widely used as catalysts in industry for producing more than 1×10^8 mt/year of products. The most commonly used are HF, H_2SO_4, $HClO_4$, and H_3PO_4 (in liquid form or supported on Keiselguhr). Solid acids have many advantages such as simplicity in handling, decreased reactor and plant corrosion problems, and more environmentally safe disposal. Also, wastes and by-products can be minimized or avoided by developing cleaner synthesis routes. On the other hand, reduction in the amount of liquid acid needed and/or simplification in handling procedures is required for risk reduction, economic advantage, and environment protection.[1] Uses of heteropolyacids (HPAs) as catalysts for fine organic synthetic processes have been developed that are very important for industries related to fine chemicals, such as flavors, pharmaceuticals, and food industries.[2] Heteropolyacids are cheap, reusable, heterogeneous, and easily available catalysts.[3] In recent years,

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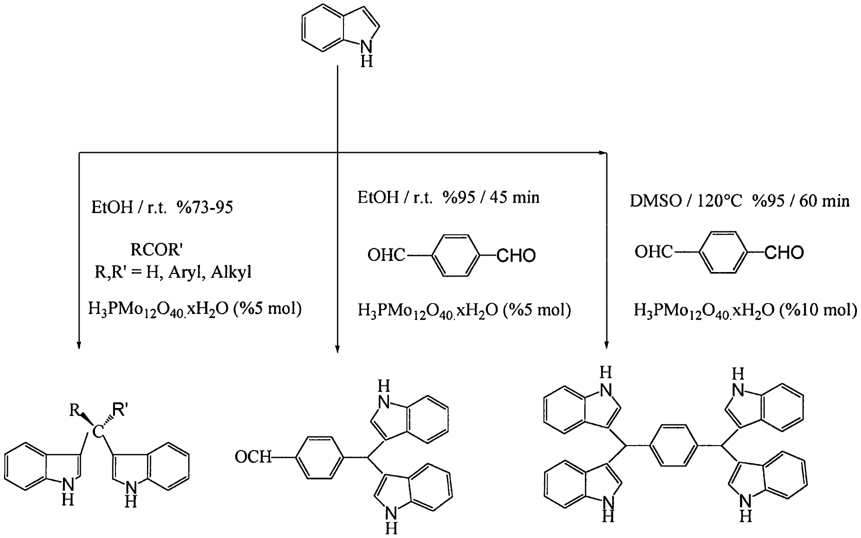
heteropolyacids and their salts have received considerable attention as powerful reaction mediums for effecting various organic transformations[3] such as selective bromination of aromatic compounds, silylation of alcohols, oxidation of aromatic amines to nitro compounds, thioacetalization and transthioacetalization reactions, oxidation of hydroxy groups to their corresponding carbonyl functions, *gem*-acylation,[4] and Friedel-Crafts[5] reactions. The use of Lewis acids in the synthesis of bis-indolyl methanes is also well known.[6] Lewis acids such as $AlCl_3$ and $LiClO_3^7$, I_2^8 have been used for this purpose. However, the reaction can also be assisted by IR irradiation using a bentonitic clay as catalyst under solvent-free conditions.[9] The above-mentioned applications of Lewis acids suffer from two limitations. First, more than stoichiometric amounts of the Lewis acid are needed in many cases. Second, these Lewis acids are moisture sensitive and easily decomposed and deactivated in the presence of even a small amount of water. Recently, lanthanide and indium triflates were reported as effective catalysts in the reaction of indoles with aldehydes or ketones.[10] While these salts are active in aqueous solution, longer reaction times (12–36 h) are required to obtain the desired product in good yield. Furthermore, lanthanide triflates are highly expensive. During the course of our work towards the application of solid acids in organic reactions[11] we found that $H_3PMo_{12}O_{40}{\cdot}xH_2O$ is an efficient catalyst for the condensation of indole and aldehyde or ketones. Here we wish to report a rapid and convenient procedure for the preparation of bis-indolyl methanes from indole and aldehydes or ketones in the presence of $H_3PMo_{12}O_{40}{\cdot}xH_2O$ in ethanol (Scheme 1 and Table I).

The reaction of benzaldehyde and indole in the presence molybdatophosphoric acid (5% eq) was complete after 20 min in ethanol as solvent at room temperature (entry 1). Both aromatic and heterocyclic aldehydes reacted similarly to give the corresponding bis-indolyl derivatives in high yields and short reaction times (entries 1–7 and 10). Aliphatic aldehyde and ketones reacted smoothly providing the corresponding products in good-to-moderate yields (entries 8, 9, 11). The reaction of 3-nitrobenzaldehyde was complete after 2 h but 4-nitrobenzaldehyde produced the corresponding bis-indolyl methane's after 6 h. Interestingly, when we used terephetalaldehyde, *p*-bis-indolylmethane benzaldehyde was produced in excellent yield (Scheme 1). Also *p*-di(bis-indolylmethane)benzene was obtained in dimethyl sulfoxide (DMSO) as solvent at 120°C after 1 h in high yield.

In conclusion, the cheapness and ready availability of the catalyst, easy and clean workup, and good yields make this method attractive for organic chemists.



SCHEME 1

EXPERIMENTAL

General

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. Yields refer to isolated pure products. Products were characterized by comparison of their spectral (IR, ^{1}H NMR), thin layer chromatography (TLC), and physical data with authentic samples.

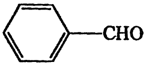
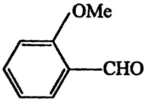
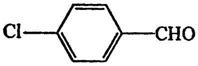
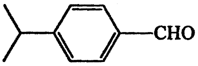
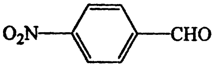
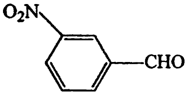
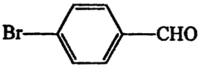
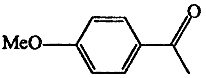
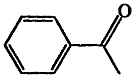
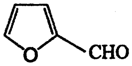
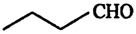
General Procedure for Mono Bis-Indolylmethanes

$H_3PMo_{12}O_{40} \cdot xH_2O$ (0.05 mmol) was added to the stirring solution of indole (2 mmol), aldehyde, or ketone (1 mmol) in EtOH (5 ml) at room temperature. The reaction was followed by TLC. On completion H_2O (20 mL) was added to the reaction mixture. The products were precipitated and filtered. Then the residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate: 8:2).

Typical Procedure for 1,4-Phenylene-di(bis-indolylmethane)

The mixture of indole (4 mmol), terephethalaldehyde (1 mmol), and $H_3PMo_{12}O_{40} \cdot xH_2O$ (0.10 mmol) in DMSO (10 ml) was heated to 120°C. Reaction was complete after 1 h (monitored by TLC). H_2O (30 ml) was

TABLE I Preparation of Bis-Indolyl Methanes from Indole and Aldehydes or Ketones in the Presence of $H_3PMo_{12}O_{40}$ as a Catalyst in Ethanol at Room Temperature

Entry	Substrate	Time (h)	Isolated yield (%)
1		0.33	93
2		0.18	92
3		1	90
4		0.5	95
5		6	90
6		2	91
7		2	92
8		10	81
9		15	73
10		0.5	80
11		18	90

added to the reaction mixture. The red product precipitated and was isolated by filtration. Then the residue was washed with diethyl ether. Pure p-di(bis-indolylmethane) benzene was obtained.

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