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Diammonium Hydrogen Phosphate as an Efficient and Inexpensive Catalyst for the Synthesis of Bis(indolyl)methanes under Solvent-Free Conditions

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Summary. Bis(indolyl)methanes were synthesized by the reaction of indole derivatives and aromatic and aliphatic aldehydes in the presence of diammonium hydrogen phosphate as a solid catalyst under solvent-free conditions. This methodology offers significant improvements for the synthesis of bis(indolyl)methanes with regard to the yield of products, simplicity in operation, and green aspects by avoiding toxic catalysts and solvents.

Keywords. Indole; Heterocycle; Solvent-free; Aldehyde.

Introduction

Indole and its derivatives are important intermediates in organic synthesis and exhibit various physiological properties and pharmacological activities [1], such as beneficial estrogen metabolism promoter [2], inhibitory of human prostate cancer cells [3], and radical scavenging activities associated with cancer cells [4]. These compounds are also used as dietary supplements, which promote healthy estrogen metabolism in human by converting both estrone and estradiol to their respective 2-hydroxy derivatives [5]. Over the past decade, a number of natural products containing bis(indolyl)methanes (*BIM*s) have been isolated from marine sources indeed [6]. Therefore, there is a great deal of interest in the synthesis of these class of compounds.

The methods which are used are based on the reaction of indole and aldehydes or ketones catalyzed by an acidic catalyst. There are several catalysts reported that promote this reaction, such as protic acids [7], *Lewis* acids [8, 9], heterogeneous acidic catalysts [10–13], and reagents like iodine [14], *NBS* [15], *CAN* [16], and hexamethylenetetramine bromine [17]. However, many of these methods still suffer from some drawbacks, such as long reaction time, expensive reagents, low yields of products in some cases, high catalyst loading, corrosive reagents, and large amounts of solid supports, which would eventually result in the generation of large amounts of toxic waste. For these reasons, superior catalysts, which are cheap, less toxic, easily available, air stable, and water-tolerant are desirable.

In continuation of our interest in the synthesis of heterocyclic compounds [18] we examined diammonium hydrogen phosphate (*DAHP*) [19] for the synthesis of *BIM*s under solvent free-conditions.

Results and Discussion

Initially, we carried out the reaction of indole with 4-chlorobenzaldehyde in the presence of different amounts of *DAHP* at 80°C. It was found that the best result was obtained with 30 mol% of *DAHP*. It is worthy to note that in the absence of *DAHP* the reaction did not yield any product at 80°C even after

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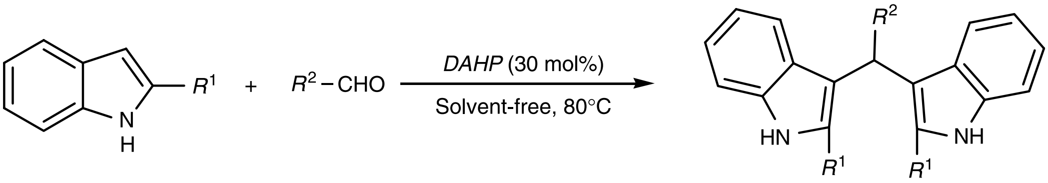

Scheme 1

Table 1. Synthesis of *BIM*s by the reaction of indole derivatives and aldehydes in the presence of *DAHP* at 80°C

Entry	Aldehyde	Indole	Time/h	Yield/%[a]	Ref.[b]
1	benzaldehyde	indole	2	87	[9]
2	4-nitrobenzaldehyde	indole	2	89	[9]
3	4-methoxybenzaldehyde	indole	2	83	[9]
4	3-nitrobenzaldehyde	indole	2	91	[9]
5	2-nitrobenzaldehyde	indole	2.5	92	[9]
6	cinnamaldehyde	indole	3	93	[9]
7	terephthaldialdehyde	indole	2	86	[9]
8	anthracene-5-carbaldehyde	indole	3.5	80	[9]
9	heptanal	indole	3.5	81	[9]
10	indole-3-carbaldehyde	indole	4	83	[11]
11	furfural	2-methylindole	3.5	84	[11]
12	pyrrole-3-carbaldehyde	2-methylindole	3.5	82	[11]
13	pyridine-2-carbaldehyde	2-methylindole	3	87	[11]
14	4-nitrobenzaldehyde	2-methylindole	3	89	[11]
15	4-methoxybenzaldehyde	2-methylindole	3	85	[12]

[a] Isolated yield. [b] The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by the procedures given in the references

a long reaction time. Thus, the work was focused on the synthesis of desired compounds with the optimized amounts of *DAHP* (30 mol%) under solvent-free conditions at 80°C (Scheme 1).

As shown in Table 2, a series of aromatic, aliphatic, and heterocyclic aldehydes underwent the electrophilic substitution reaction with indole smoothly to afford a wide range of substituted *BIM*s in good to excellent yields. Many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency by using this procedure. Furthermore, even an unsaturated aldehyde (cinnamaldehyde) gave the corresponding *BIM* without polymerization (Table 1, entry 6). The heterocyclic aldehydes also worked well without the formation of any side products (Table 1, entries 10–13). The work-up procedure was very simple including addition of cold water at the end of the reaction to the mixture and filtration of the product.

In conclusion, we showed that *BIM*s can be synthesized by a simple and highly efficient electrophilic substitution of indoles with aldehydes using *DAHP* as an efficient and broadly available catalyst. The mildness of the reaction conditions, low cost of the reagents, and ease of work-up make the present methodology useful for the synthesis of compounds in drug discovery studies.

Experimental

Melting points were obtained in open capillary tubes and were measured on an electrothermal 9200 apparatus. Mass spectra were recorded on a Shimadzu QP 1100 BX mass spectrometer. IR spectra were recorded on KBr pellets on a Shimadzu IR-470 spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker 300 DRX Avance instrument at 300 and 75 MHz.

General Procedure for the Synthesis of BIMs

Aldehyde (2 mmol), and 1 mmol indole were mixed with 0.396 g *DAHP* (0.3 mmol) and placed in a round bottomed flask. The mixture was stirred at 80°C. After the completion of the reaction confirmed by TLC (eluent: *n*-hexane/ethyl acetate = 3/1), cold H_2O was added to the mixture and the precipitated product was separated by simple filtration. Finally, the crude product was recrystallized from ethyl acetate/*n*-hexane or ethanol.

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