

Preparation of Indolylmethanes Catalyzed by Metal Hydrogen Sulfates

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Solid acids were developed and applied to the condensation reactions of indole with carbonyl compounds at ambient temperature. Tetra-(indolyl)methanes were obtained by the condensation reaction of indole with dialdehyde compounds.

Keywords: Solid acids, *Bis*(indolyl)methanes, Carbonyl compounds, Indole, Tetra(indolyl)methanes, Aldehydes, Ketones

INTRODUCTION

In industry, acids are widely used as catalysts to produce more than 1×10^8 Mt of chemicals per year [1]. The most commonly used are HF, H₂SO₄, HClO₄, and H₃PO₄ (in liquid form or supported on Keiselguhr). Solid acids have many advantages such as simplicity of handling, fewer reactor and plant corrosion problems, and environmentally safer disposal in different chemical processes. Also, wastes and by-products can be minimized or avoided by using solid acids, thereby developing cleaner synthesis routes. On the other hand, any reduction in the amount of liquid acid needed and/or any simplification in handling procedures is required for risk reduction, economic advantage and environmental protection [2], and using an applicable industrial catalyst that is safe, eco-friendly, green and simply recycled in reaction mixtures has commanded much attention. Thus, green chemistry has been defined as a set of principles that reduces or eliminates the use or generation of hazardous substances throughout the entire life of chemical materials.

Solid inorganic acidic salts, such as metal hydrogen sulfates, play a prominent role in organic synthesis under

heterogeneous conditions. Along this line, using Al(HSO₄)₃ [3], Fe(HSO₄)₃ [4], Mg(HSO₄)₂ [5], NaHSO₄.H₂O [6], and Oxone[®] (2KHSO₅.KHSO₄.K₂SO₄) [7], which are low in toxicity, highly stable toward humidity, recyclable and air stable have found more attention. In continuation of our studies on the use of inorganic hydrogen sulfate acidic salts in organic transformations [3-7], we have found that aluminum hydrogen sulfate is suitable for the direct synthesis of *bis*(indolyl)- and tetra(indolyl)methanes at room temperature.

Indole and its derivatives are important intermediates in organic synthesis and exhibit various physiological properties and pharmacological activities [8]. Over the past decade, a number of natural products containing *bis*(indolyl)methanes or *bis*(indolyl)ethanes have been isolated from marine sources [9]. *Bis*(indolyl)methanes are found in cruciferous plants and are known to promote beneficial estrogen metabolism [10] and induce apoptosis in human cancer cells. Therefore the preparation of these intermediates has received increased attention from synthetic organic chemists and biologists. The acid-catalyzed reaction of electron rich heterocyclic compounds with *p*-dimethylaminobenzaldehyde is known as the Ehrlich test [11] for π -electron rich heterocycles such as pyrroles and indoles. The analogous reaction of indoles with other aromatic or aliphatic aldehydes and ketones produces

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azafulvenium salts. The azafulvenium salts can undergo further addition with a second indole molecule to afford *bis(indolyl)ethanes* [12]. Generally, this reaction is promoted using protic acids [13], Lewis acids [14], heteropoly acids [15], and heterogeneous catalysts (clay, zeolites, and supported reagents [16]). Other catalysts such as iodine [17], CAN [18], potassium hydrogen sulfate [19], triphenyl phosphonium perchlorate [20], NBS [21], and hexamethylenetetramine bromine [22] have also been used to catalyze this reaction. This reaction also proceeds in ionic liquids such as 1-butyl-3-methylimidazolium tetrafluoroborate and 1-butyl-3-methylimidazolium hexafluorophosphate [23] or in the solid-state by employing a high-pressure mercury lamp [24]. Recently, rare-earth perfluorooctanoates [RE(PFO)₃] [25], trichloro-1,3,5-triazine [26], zirconium tetrachloride [27], ZrOCl₂.8H₂O/silica gel [28], AlW₁₂PO₄₀ [29], and ionic liquids in conjunction with In(OTf)₃ or FeCl₃.6H₂O [30] were employed for this transformation.

Although these methods are suitable for certain syntheses, some drawbacks such as long reaction time (*e.g.* 10 days [13c]), expensive reagents (*e.g.* dyspersium triflate [14d]), low yields of products in some cases, high catalyst loading, corrosive reagents, and large amounts of solid supports eventually result in the generation of a large amount of toxic waste. For this reason, superior catalysts, which are inexpensive, less toxic, easily available, air-stable, recyclable and water-tolerant, are desirable.

EXPERIMENTAL

General

Chemicals were purchased from Merck, Fluka and Aldrich chemical companies. IR spectra were run on a Shimadzu infra red spectroscope (IR-435). The ¹H NMR and ¹³C NMR spectra were obtained on a JEOL NMR spectrometer, model FX 90Q. Melting points were recorded on a Melting Point SMP1 apparatus in open capillary tubes and are uncorrected. With TLC, using silica gel SILG/UV 254 plates, the progress of reactions was followed. The *bis(indolyl)methane* products were characterized by comparison of their spectral (IR, ¹H NMR), TLC and physical data with the authentic samples [14-16,27].

Synthesis of *Bis(indolyl)methanes* 3

A mixture of indole **1** (2 mmol), aldehyde or ketone (1 mmol), and inorganic hydrogen sulfate acidic salts (1 mmol) in ethanol (4 ml) was magnetically stirred at room temperature. After completion of the reaction, as confirmed by TLC, the reaction mixture was filtered. The residue was washed with EtOH (2 × 4 ml). Then, water (25 ml) was added to the filtrate and the precipitate was filtered. The product was purified by column chromatography on silica gel [eluent: EtOAc/*n*-hexane (10:90)] to give pure *bis(indolyl)methanes*.

Synthesis of Tetra(indolyl)methane 5

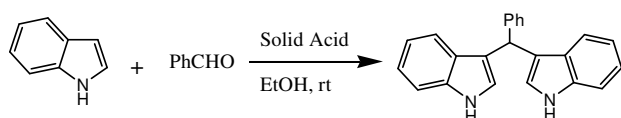
A mixture of indole **1** (4 mmol, 0.468 g), terephthaldehyde (**4**) (1 mmol, 0.134 g), and Al(HSO₄)₃ (2 mmol, 0.636 g) in DMSO (5 ml) was heated on an oil bath at 120 °C. The reaction mixture was filtered after 1 h. The residue was washed with EtOH (2 × 4 ml). Then, water (40 ml) was added to the filtrate, and the precipitate was filtered. The product was purified by column chromatography on silica gel [eluent: EtOAc/*n*-hexane (10:90)] to give pure tetra(indolyl)methanes 0.492 g, 87% yield.

RESULTS AND DISCUSSION

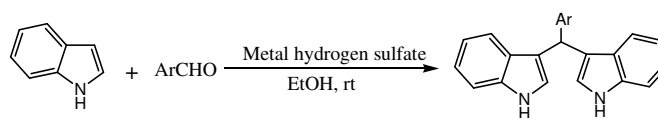
In continuation of our studies on the application of heterogeneous systems [2-7] we were interested in using inorganic solid acids such as Oxone[®], silica sulfuric acid, and metal hydrogen sulfate acidic salts, including Ca(HSO₄)₂, Zn(HSO₄)₂, Mg(HSO₄)₂, Al(HSO₄)₃, as catalysts in the synthesis of *bis(indolyl)methanes*. This is a simple method for the effective synthesis of *bis(indolyl)methanes*, obtained from the reaction of indole and a carbonyl compound, under mild and heterogeneous conditions at room temperature, in ethanol as a solvent (Scheme 1).

In a preliminary study, the effect of some solid acids on the yields of *bis(indolyl)methane* was investigated with the reaction of benzaldehyde with indole as a model compound. As shown in the Table 1, Al(HSO₄)₃ is a more suitable solid acid catalyst for this condensation reaction in ethanol at room temperature. Mg(HSO₄)₂, Ca(HSO₄)₂, and Zn(HSO₄)₂ also catalyze this condensation but with longer reaction times. Although this reaction was fast in the presence of Oxone[®] and

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Scheme 1



Metal hydrogen sulfate: $\text{Zn}(\text{HSO}_4)_2$, $\text{Mg}(\text{HSO}_4)_2$, $\text{Ca}(\text{HSO}_4)_2$

Scheme 2

Table 1. Effect of Inorganic Solid Acidic Salts^a on the Condensation of Indole^b and Benzaldehyde^c in Ethanol to Give Phenyl-3,3'-Diindolylmethane

Entry	Catalyst	Time (h)	Yield (%) ^c
1	$\text{Mg}(\text{HSO}_4)_2$	6.0	89
2	$\text{Ca}(\text{HSO}_4)_2$	3.5	91
3	$\text{Zn}(\text{HSO}_4)_2$	3.0	91
4	$\text{Al}(\text{HSO}_4)_3$	2.5	92
5	Silica sulfuric acid	2.0	-
6	Oxone [®]	2.75	-

^a1 mmol. ^b2 mmol. ^c1 mmol. ^dAt room temperature. ^eIsolated yields.

Table 2. $\text{Al}(\text{HSO}_4)_3$ Catalyzed Condensation Reactions of Indole with Various Carbonyl Compounds to Synthesize the Corresponding Bis(indolyl)methanes

Entry	R ₁	R ₂	Time (h)	Yield (%) ^a
1	Ph	H	2.5	92
2	4-FC ₆ H ₄	H	2.25	91
3	4-ClC ₆ H ₄	H	2.0	93
4	4-BrC ₆ H ₄	H	2.0	91
5	4-MeOC ₆ H ₄	H	1.1	90
6	2-HO-C ₆ H ₄	H	1.75	92
7	3-NO ₂ C ₆ H ₄	H	3.75	90
8	4-NO ₂ C ₆ H ₄	H	5.25	92
9	2,6-Cl ₂ C ₆ H ₃	H	1.75	92
10	PhCH=CH	H	3.0	87
11	4-pyridine	H	4.5	88
12	<i>n</i> -C ₃ H ₇	H	3.0	83
13	Ph	CH ₃	5.25	73
14	Cyclohexanone	-	4.0	71

^aIsolated yield after purification.

silica sulfuric acid, a mixture of products were detected that make work up difficult.

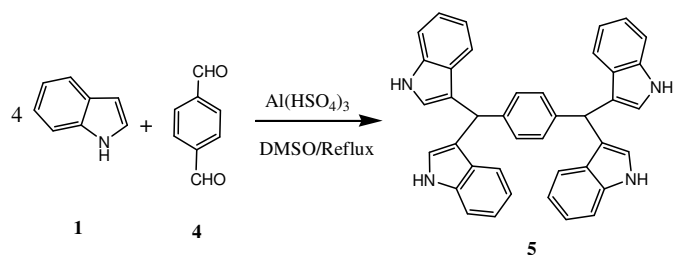
Next, we examined the catalytic ability of these inorganic solid acidic salts for the condensation reaction of indole with other carbonyl compounds in order to show the general application of the method. The catalysts promote the reactions efficiently. One mmol of the catalyst was sufficient to mediate the reactions toward the formation of the corresponding bis(indolyl)methanes in excellent yields within 1.5-12 h. The lower quantities of these solid acids (i.e. 0.5 mmol) also gave satisfactory results at longer reaction times.

A variety of carbonyl compounds reacted smoothly with indole to produce bis(indolyl)methanes in the presence of $\text{Al}(\text{HSO}_4)_3$ as a catalyst at room temperature in EtOH (Scheme 2). The results are listed in Table 2. In all cases, aldehydes reacted more rapidly and gave higher yields than ketones. The nature of the substituents on the aromatic ring showed some effects on this conversion. On the other hand, the electron rich substitutes (OH, OCH₃) required shorter reaction times than their electron-deficient counterparts, such as NO₂. In addition, the aliphatic aldehydes *n*-butanal afforded an 83% yield in 3.0 h. Ketones required longer reaction times and gave lower yields, which is most probably due to the steric effects of the alkyl group (Table 2, Entries 13, 14).

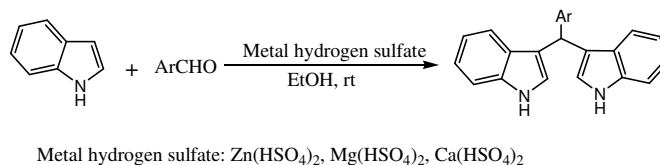
This reaction was further explored for the synthesis of tetraindolyl compounds **5**, by the condensation of terephthalaldehyde **4** with four equivalents of indole under similar conditions in very good yields (Scheme 3).

We also investigated the condensation reaction of indole with carbonyl compounds in the presence of other inorganic metal hydrogen sulfates including $\text{Mg}(\text{HSO}_4)_2$, $\text{Ca}(\text{HSO}_4)_2$, and $\text{Zn}(\text{HSO}_4)_2$ (Scheme 4). The results are summarized in Table 3.

In conclusion, inorganic solid acidic salts have been employed for the synthesis of bis(indolyl)methanes and tetra(indolyl)methanes by the electrophilic substitution



Scheme 3



Scheme 4

Table 3. Condensation Reaction of Indole with Aldehydes in the Presence of Metal Hydrogen Sulfates at Room Temperature

Entry	Carbonyl compound	$\text{Zn(HSO}_4)_2$		$\text{Mg(HSO}_4)_2$		$\text{Ca(HSO}_4)_2$	
		Time (h)	Yield (%) ^a	Time (h)	Yield (%) ^a	Time (h)	Yield (%) ^a
1		3.0	91	6.0	89	3.5	91
2		3.5	90	8.0	90	4.0	92
3		2.5	91	7.5	89	3.0	91
4		2.5	90	7.5	90	3.0	93
5		2.0	88	6.0	88	2.5	87
6		1.75	90	5.0	89	2.0	89
7		1.75	88	5.0	90	2.0	90
8		3.5	90	7.0	88	4.0	89
9		6.0	88	10.0	88	7.0	90
10		4.5	86	8.0	87	5.5	87
11		6.0	87	10.0	86	6.5	90

^aIsolated yields.

reaction of indole with aldehydes or ketones. This method is applicable to a wide range of aldehydes, including aromatic, aliphatic, α,β -unsaturated and heterocyclic substrates, and ketones. The attractive features of this procedure are the mild reaction conditions, high conversions, cleaner reaction profiles, and the use of environmentally friendly catalysts.

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