

Synthesis of *Bis*(indolyl)methanes in Presence of Anhydrous Copper(II) Sulfate

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This work reports the improved procedure for the preparation of *bis*(indolyl)methanes from the corresponding aldehydes and indole. Anhydrous copper(II) sulfate efficiently promotes the chemoselective synthesis of *bis*(indolyl)methanes *via* electrophilic substitution reactions of indole with aldehydes. The reaction was carried out in refluxing dichloromethane or microwave-assisted solvent-free conditions. The adducts were produced in good to excellent yields.

Key Words: Anhydrous copper(II) sulfate, *Bis*(indolyl)methanes, Electrophilic substitution, Microwave irradiation, Solvent-free.

INTRODUCTION

Indoles and their derivatives are important group of heterocyclic compounds, which play a fundamental role in organic and bioorganic chemistry¹⁻³. Because of their existence in biologically active natural products as well as their application as antibiotics in the field of pharmaceuticals, there is significant interest in the synthesis of these compounds in recent years. This reaction involves addition of two nucleophiles to a carbonyl group, like coupling of two molecules of phenol with formaldehyde, leading to diarylmethanes. The acid-catalyzed reaction of indoles with aromatic and aliphatic aldehydes and ketones produces azafulvenium salts which undergo further addition with the second molecule of indole to afford *bis*(indolyl)methanes⁴. Although it was discovered in the beginning of the 20th century, this reaction was nearly forgotten (the second mentioned in 1957). Beilstein Crossfire database reveals now around 38 references on the reaction between unsubstituted indole and arbitrary carbonyl compounds, leading to the *bis*(3-indolyl)-methanes. Among these papers, 34 are published after 2000, which means the growing interest to this reaction⁵⁻⁴⁶.

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Anhydrous copper(II) sulfate can function as a convenient medium and also act as a Lewis acid either in solvent and/or in solvent-free conditions. Due to their availability, cheapness and low toxicity, copper salts have recently attracted much attention. Recently we reported a procedure for chemoselective dithioacetalization of aldehydes in a solvent and/or under solventfree conditions using anhydrous copper sulfate⁴⁷. Since there are no reports on the microwave-assisted *bis*(indolyl)methane synthesis, it will be worthwhile to study this reaction under microwave irradiation. Herein we report an efficient, clean, fast and mild method for chemoselective reaction of indole with aldehydes in solvent and under solvent-free conditions with microwave irradiation using anhydrous copper(II) sulfate.

EXPERIMENTAL

IR spectra of the compounds were taken as thin films for liquid compounds and as KBr pellets for solids on a Nicolet spectrometer (Magna 550). A Bruker (DRX-500 Avance) NMR was used to record the ¹H NMR spectra. All NMR spectra were determined in CDCl₃ at ambient temperature. The microwave oven used for this work was ETHOS-MR (800 W, 140 °C) at 2450 MHz. Melting points were determined on a Buchi B540 apparatus.

General synthesis for *bis*(indolyl) methane in dichloromethane: The anhydrous copper(II) sulfate (0.8 g) was added to a stirring solution of indole (2 mmol) and aldehyde (1 mmol) in CH₂Cl₂ (15 mL). The resulting mixture was stirred at refluxing temperature for appropriate time as required for completion of the reaction (Table-1), which was monitored by TLC (petroleum ether:ethyl acetate, 4:1). After separation of the catalyst by filtration, the solvent was removed under reduced pressure. The pure products were obtained by column chromatography on silica gel or PTLC.

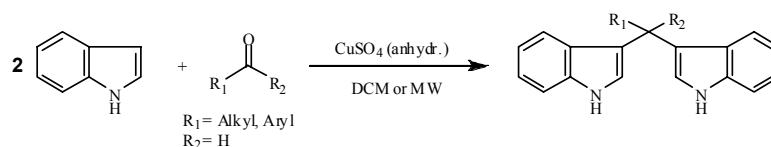
General procedure for microwave irradiation: To a solution of aldehyde (1 mmol) and indole (2 mmol) in dichloromethane (5 mL) was added 0.8 g anhydrous copper(II) sulfate. After evaporation of the solvent under vacuum, the solid residue was placed in a teflon flask (*ca.* 20 mL) and subjected to microwave irradiation for appropriate time (Table-1). The reaction mixture was extracted with dichloromethane and was purified by column chromatography on silica gel or PTLC.

Selected ¹H NMR data: **3a:** m.p. 92-94 °C; ¹H NMR (CDCl₃, 500 MHz): δ 5.75 (s, 1H), 6.59 (s, 2H), 7.12 (t, 2H, *J* = 7.3 Hz), 7.26 (t, 2H, *J* = 7.5 Hz), 7.3-7.38 (m, 5H), 7.44 (d, 2H, *J* = 7.6 Hz), 7.49 (d, 2H, *J* = 7.9 Hz), 7.8 (br s, 2H). **3l:** m.p. 172-174 °C; ¹H NMR (CDCl₃, 500 MHz): δ 2.15 (s, 6H), 7.05 (t, 2H, *J* = 7.8 Hz), 7.13- 7.21 (m, 4H), 7.32 (d, 2H, *J* = 7.8 Hz), 7.43 (d, 2H, *J* = 7.7Hz), 7.84 (br s, 2H).

RESULTS AND DISCUSSION

The present investigations showed that indole reacts solely with aldehydes in the presence of anhydrous copper(II) sulfate. The corresponding *bis(indolyl) methanes* were obtained in good to excellent yields.

Anhydrous copper(II) sulfate is a mild, efficient and cheap medium for the synthesis of *bis(indolyl)methanes* from aliphatic as well as aromatic aldehydes. Any effort for the synthesis of *bis(indolyl)methanes* by the reaction of indole and ketones in the presence of copper(II) sulfate was failed. The reactions were carried out in solvent and microwave-assisted solvent-free conditions (**Scheme-I**). The results are summarized in Table-1. All products were characterized by m.p., IR, ^1H NMR and their physical data were similar to those reported in literature.



Scheme-I

TABLE-1
ANHYDROUS COPPER(II) SULFATE MEDIATED SYNTHESIS OF
BIS(INDOLYL)METHANE UNDER VARIOUS CONDITIONS

Entry	R ₁	R ₂	Time (h) / Yield (%)	Time (min) / Yield (%)
			CH ₂ Cl ₂ solvent	MW solvent-free condition
a	C ₆ H ₅	H	2.0/85	4/87
b	4-BrC ₆ H ₄	H	1.5/92	4/93
c	4-ClC ₆ H ₄	H	1.5/93	4/91
d	4-CH ₃ C ₆ H ₄	H	2.5/81	4/90
e	4-CH ₃ OC ₆ H ₄	H	5.0/85	4/82
f	2-HOC ₆ H ₄	H	3.0/84	4/80
g	4-NO ₂ C ₆ H ₄	H	1.5/94	4/92
h	2-NO ₂ C ₆ H ₄	H	1.5/87	5/87
i	Furyl	H	2.0/87	5/79
j	CH ₃ (CH ₂) ₄	H	7.0/76	5/72
k	CH ₃ (CH ₂) ₅	H	7.0/75	5/72

Initially, the entitled reaction in dichloromethane (DCM) as a solvent was investigated. In a typical procedure, benzaldehyde (1 mmol) with indole (2 mmol) in the presence of anhydrous copper(II) sulfate (0.8 g) at refluxing temperature afforded the desired *bis(indolyl)methane* in 85 % yield. The reaction was then applied to a variety of aromatic and aliphatic

aldehydes. Aromatic aldehydes reacted more efficiently than aliphatic aldehydes. In spite of electron donating groups, electron withdrawing substituents on aromatic ring cause a slight decrease in reaction time and higher yield (entries b, c, g, h Table-1). Although the reaction of aliphatic aldehydes and indole in the presence of anhydrous copper(II) sulfate promoted at higher reaction time, the reaction of ketones and indoles didn't occur (entries j, k, Table-1).

In addition, the reactivity of carbonyl compounds and indole was studied in microwave-assisted solvent-free conditions. As expected, microwave-assisted solvent-free conditions proceeded in high yields and short reaction times. The best results were obtained by electron withdrawing substituent on aromatic ring (entries b, c, g, h, Table-1).

In summary, anhydrous copper(II) sulfate has been demonstrated to be a mild and efficient system for the chemoselective electrophilic substitution reaction of indole with aliphatic and aromatic aldehydes. The reaction was carried out under different reaction conditions.

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