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Efficient synthesis of bis(indol-3-yl)methanes catalyzed by silicotungstic acid under ultrasound irradiation

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ABSTRACT: Synthesis of bis(indol-3-yl)methanes catalyzed by silicotungstic acid ($SiO_2 \cdot 12WO_3 \cdot 24H_2O$) was carried out in 50-97% yield within 15-120 min in EtOH at r. t. under ultrasound irradiation.

Key words: Catalysts；Electrophilic substitutions；Heterocycles；Heterogeneous catalysis；Sonication

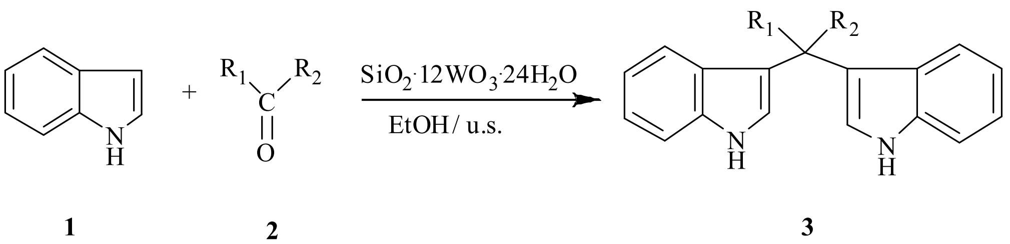
INTRODUCTION

Indoles and their derivatives are important intermediates in organic synthesis in view of their pharmacological activities[1]. Bis(indol-3-yl)methane (BIM) derivatives affect the central nervous system and so are used as tranquilizers. BIM can increase the body's natural metabolism of hormones and promote good estrogen (2-hydroxyestrogen). Its effect in the prevention of cancer due to its ability to modulate certain cancer causing estrogen metabolites[2]. BIM can induce apoptosis in human cancer cells and may also normalize abnormal cell growth associated with cervical dysplasia[3]. Over the past few years, BIM have been obtained by reaction of indoles with various aldehydes or ketones in the presence of either protic or Lewis acids [4]. Recently, the reactions were carried in acetonitrile in the presence of many kind of catalyst, such as $InCl_3$, $In(OTf)_3$ [5], $PPh_3 \cdot HClO_4$ [6], I_2 [7], Zeolite [3], and TCT (trichloro-1,3,5-triazine)[8]. However, the acetonitrile is not an environmentally friendly solvent and therefore environmentally friendly, and cheaper solvent is desirable.

Heteropolyacids are found to act as outstanding catalysts in electrophilic transformations[9].

Silicotungstic acid is a solid heteropolyacid，which has been used for the synthesis of trioxanes [10], alkylation of benzene with olefins [11], production of acrolein from glycerol [12] and cyclodehydration of 1,4-butanediol to tetrahydrofuran [13]. The results reported in literatures have shown that silicotungstic Acidhas high catalytic activity and good stability, and is an environmentally friendly catalyst. Murugan et al have reported that synthesis of bis(indol-3-yl)pyrazolyl methanes (from indole and pyrazolyl aldehydes) and 3-alkylated indoles catalyzed by silicotungstic acid was carried out in good yields [14].

Ultrasound has increasingly been used in organic synthesis in the last three decades. Compared with



Scheme 1 Synthesis of bis(indol-3-yl)methanes

traditional methods, the ultrasonic procedure is more convenient and can be carried out in higher yields, shorter reaction time or milder conditions [15]. Zeng et.al have reported synthesis of unsymmetrical bis(indol-3-yl)alkanes catalyzed by ceric ammonium nitrate (CAN) under ultrasonic irradiation [16]. Our laboratory has also described the preparation of BIM catalyzed by aminosulfonic acid under ultrasound irradiation [17]. Herein, an efficient synthesis of bis(indol-3-yl)methanes catalyzed by silicotungstic acid in EtOH under ultrasound irradiation is reported (**Scheme 1**).

EXPERIMENTAL

Liquid substrates were distilled before use. Melting points were uncorrected. ^{1}H NMR was measured on a Bruker AVANCE 400 (400 MHz) spectrometer using TMS as the internal standard. Sonication was performed in Shanghai Branson-CQX ultrasonic cleaner (with a frequency of 25 kHz and a nominal power 250 W) and SK 250 LH ultrasonic cleaner (with a frequency of 40 kHz, and a nominal power 250 W; Shanghai Kudos Ultrasonic Instrument Co., Ltd.). The reaction flask was located in the cleaner, where the surface of reactants was slightly lower than the level of the water. Observation of the surface of the reaction solution during vertical adjustment of vessel depth showed the optimum position by the point at which maximum surface disturbance occurred. The reaction temperature was controlled by addition or removal of water from ultrasonic bath.

*General procedure:*Indole (**1**, 1 mmol), aldehydes or ketones (**2**, 0.5 mmol), anhydrous ethanol (5 mL), Silicotungstic acid (0.05 mmol), were mixed in a 50 mL round flask. The reaction mixture was irradiated in water bath of an ultrasonic cleaner at 20-22 °C for the period as indicated in Table 2. After the completion of the reaction, the reaction mixture was diluted with H_2O (5 mL) and extracted three times with ethyl acetate (3×15 mL). The combined organic layers were dried over anhyd $MgSO_4$. and filtrated. And then the solvent from the extract was evaporated under reduced pressure to give the residue, which was purified by column chromatography on silica gel (200-300 mesh), eluted with petroleum ether or mixture of petroleum ether/diethyl ether. Their IR, ^{1}H NMR, and elemental analysis data established the structure of **3f** and **3h** compounds. The authenticity of the rest compounds was established by comparing their melting point with literatures.

3,3'-((3-chlorophenyl)methylene)bis(1*H*-indole) (**3f**) , m.p. 81-83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.15 (s, 1H, Ar_3CH), 6.67(s, 2H), 7.04 (t, 2H, J=7.8 Hz), 7.11-7.45 (m, 10H), 7.96 (s, 2H, NH). IR (KBr) v: 3412, 3052, 1610 cm^{-1}. Anal. calcd for $C_{23}H_{17}N_2Cl$: C 77.53, H 4.77, N 7.87; found C 77.45, H 4.71, N 7.82.

3,3'-((2,4-dichlorophenyl)methylene)bis(1*H*-indole) (**3h**), m.p. 141-143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.30 (s, 1H, Ar_3CH), 6.64(s, 2H), 7.06 (t, 2H, J = 7.6 Hz), 7.09-7.41 (m, 8H), 7.48 (s, 2H), 7.93 (s, 2H, NH). IR (KBr) v: 3420, 3055, 1600 cm^{-1}. Anal. calcd for $C_{23}H_{16}N_2Cl_2$: C 77.77 , H 4.10, N 7.18; found C 77.59, H 4.21, N 7.22.

RESULTS AND DISCUSSION

The effect of the reaction conditions on the reaction of indole with aromatic aldehydes and ketones under ultrasound irradiation was summarized in **Table 1**.

When the amount of catalyst (silicotungstic acid) was 0.005 mmol, the yield of 3,3'-((4-chlorophenyl) methylene)bis(1*H*-indole) was only 69%. Increasing the amount of silicotungstic acid to 0.01, 0.025, 0.05 mmol, the yield of 3,3'-((4-chlorophenyl) methylene)bis(1*H*-indole) increased to 77%, 85%, 96%, respectively. Increasing the catalyst to 0.075 and 0.1 mmol caused a decrease in the yield to 83% and 76%. Therefore, we chose 0.05 mmol as the amount of catalyst for the synthesis of title compounds.

We also observed the effect of different irradiation frequencies on the reaction. When the frequency of ultrasound irradiation was 25 kHz, the yield of 3,3'-((4-chlorophenyl)methylene)bis(1*H*-indole) was 96% (**Table 1**, **Entry 4**) within 20min. With 40 kHz frequency, the yield of 3,3'-((4-chlorophenyl) methylene)bis(1*H*-indole) was 91% (**Table 1,Entry 7).** It seems that the lower frequency of ultrasound irradiation can improve the yield of 3,3'-((4-chlorophenyl)methylene)bis(1*H*-indole).

Perhaps as the ultrasonic frequency is increased, the production of cavitation in liquids decreases [16].

We also did the experiment without ultrasound irradiation; the mixture of indole with 4-chlorbenzaldehyde was stirred in ethanol for 20 min to produce 3,3'-((4-chlorophenyl)methylene) bis (1*H*-indole) in 82% yield (**Table 1**, **Entry 8**), whereas under ultrasound in the same time, 3,3'-((4-chlorophenyl)methylene)bis(1*H*-indole) was obtained in 96% yield (**Table 1**, **Entry 4; Table 2, Entry 3g**).The reaction of indole with 3-nitroacetophenone (**2n**) gave **3n** (Table 2, **Entry 3n**) in 79% yield within 2 h under ultrasound irradiation, while **3n** was obtained in 59% using stirring alone. It was clear that the ultrasound could accelerate the reaction of indole with aromatic aldehydes or ketones.

From the results above, the optimum reaction conditions were found to be: Indole (**1**, 1 mmol), aldehydes or ketones (**2**, 0.5 mmol), anhydrous ethanol (5 mL), silicotungstic acid (0.05 mmol). Under this reaction condition, a series of experiments for synthesis of BIM were performed under 25 kHz ultrasonic cleaner. The results are summarized in **Table 2**.

In the present procedure, aromatic aldehydes with electron-donating substituents or electron-withdrawing substituents have no effect on the yields, but the differences between aldehydes and ketones are apparently. The reactions of indole with aromatic aldehydes are going very well (**Table 2**, **3a-3k**). On the other hand the reactions of indole with aromatic ketones, are rather sluggish (**Table 2**, **3j-3p**), which could be caused by their steric hindranc.

In summary, we described a simple and convenient method for the synthesis of bis(indol-3-yl)methanes catalyzed by silicotungstic acid ($SiO_2 \cdot 12WO_3 \cdot 24H_2O$) under ultrasound irradiation.

Table 1 Effect of reaction conditions on synthesis of bis(indol-3-yl)methanes[a]

Entry	Amount of catalyst/mmol	Frequency/ kHz	Time/min	Yield/%
1	0.005	25	20	69
2	0.01	25	20	77
3	0.025	25	20	85
4	0.05	25	20	96
5	0.075	25	20	83
6	0.1	25	20	76
7	0.05	40	20	91
8	0.05	stir[b]	20	82

[a] Reaction temperature: 20-22 ^0C, substrate:$4\text{-}ClC_6H_4CHO$.

[b] Stirred without ultrasound irradiation.

Table 2 Synthesis of bis(indolyl)methanes catalyzed by silicotungstic acid under ultrasonic irradiation[a]

Entry	R_1	R_2	T/min	Product	Yield/%	M.P./^{0}C (lit.)
a	3,4-$(OCH_2O)C_6H_3$	H	15	**3a**	93	86-87(89-91) [7]
b	4-$CH_3OC_6H_4$	H	20	**3b**	82	185-187(187-189) [7]
c	4-$CH_3C_6H_4$	H	15	**3c**	97	103-105(99-101) [17]
d	C_6H_5	H	15	**3d**	96	96-98(93-95) [17]
e	2-ClC_6H_4	H	20	**3e**	87	71-73(72-74) [7]
f	3-ClC_6H_4	H	15	**3f**	95	81-83
g	4-ClC_6H_4	H	20	**3g**	96	74-75(76-77) [7]
h	2,4-$Cl_2C_6H_3$	H	20	**3h**	93	141-143
i	2-$NO_2C_6H_4$	H	30	**3i**	76	146-148(142-144) [17]
j	3-$NO_2C_6H_4$	H	30	**3j**	95	220-222(221-223) [7]
k	4-$NO_2C_6H_4$	H	30	**3k**	90	221-223(217-219) [7]
l	C_6H_5	CH_3	120	**3l**	53	189-191(191-193) [19]
m	4-ClC_6H_4	CH_3	120	**3m**	50	105-107(109-111) [17]
n	3-$NO_2C_6H_4$	CH_3	120	**3n**	79	261-263(257-259) [17]
	3-$NO_2C_6H_4$	CH_3	120	**3n**	59[b]	
o	4-$NO_2C_6H_4$	CH_3	120	**3o**	65	239-240(234-236) [20]
p	-$(CH_2)_5$-		60	**3p**	78	151-153(146) [21]

[a] Reaction temperature: 20-22 ^{0}C.

[b] Stirred without ultrasound

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