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Novel Schiff Base's Complex as a Green Catalyst for the Synthesis of Diindolylmethanes under Ultrasonics Irradiation[1]

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Abstract—A facile and convenient protocol was developed for the synthesis of diindolylmethanes in short reaction time and high yields using newly synthesized complex as an efficient recyclable heterogeneous catalyst. All synthesized compounds were characterized by IR, NMR spectra and elemental analysis.

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INTRODUCTION

It is well known that diindolylmethanes (DIMs) and related compounds exhibit a wide range of biological activities like antibacterial and antitumor properties [1]. Diindolylmethanes are the most active crucial substances for promoting beneficial estrogen metabolism in women and men [2]. DIMs increase the body's natural metabolism of hormones and promote the formation of good estrogen (2-hydroxyestrogen). This indole antioxidant is patented for alleviating symptoms of Fibromyalgia [3]. Due to the potent biological activity exhibited by various indole deriveatives, there is a continuous demand for new synthetic methods in this area. Several synthetic methods for the preparation of DIMs have been reported by using catalysts like trichloro-1,3,5-triazine [4], Zeolite [5], Zeokarb-225 [6], iodine [7], aminosulfonic acid [8], 12-tungstophosphoric acid supported on zirconia [9], oxalic acid [10], diphosphooctadecatungstic acid [11], aluminum oxide [12], and phosphated zirconia [13]. Most of these methods possess various disadvantages such as long reaction time, use of expensive Lewis acids, severe reaction conditions, excess of toxic or organic solvents, low yield, and cumbersome product isolation procedure. Therefore, it is necessary develop to further an efficient and convenient method for the synthesis of these significant scaffolds.

Herein, we report our preliminary results on the synthesis of diindolylmethanes catalyzed by synthesized Schiff base's complex.

[1] The text was submitted by the authors in English.

EXPERIMENTAL

Materials and measurements. For the ultrasonic activation ultrasound apparatus astra 3D (9.5 dm^3, 45 kHz frequency, input power with heating 305W, number of transducers, 2) from TECNO-GAZ was used. Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded on a Shimadzo IR-470 spectrometer. ^1H and ^{13}C NMR spectra were registered on a 500 MHz Bruker DRX-500 in $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal reference. Chemicals were purchased from Merck and Fluka. Elemental analyses were done on a Carlo-Erba EA1110CNNO-S analyzer and compared with the calculated values. All solvents before use were dried and distilled according to standard procedures.

Preparation of catalyst. A solution of synthesized Schiff base (2 mmol) and copper acetate (1 mmol) in EtOH (10 mL) were refluxed for the required time. The progress of reaction was controlled by TLC. After completion of the reaction, the mixture was filtered to separate the catalyst.

General procedure for the synthesis of diindolylmethanes. A solution of aldehyde (1 mmol), indole derivatives (2 mmol), and synthesized complex **III** (0.05 g) in EtOH (10 mL) were placed into an open vessel of Pyrex glass, and the mixture was irradiated in a water bath at 60°C by ultrasound (45 kHz) for the required reaction time. The progress of the reaction was monitored by TLC. When the irradiation was

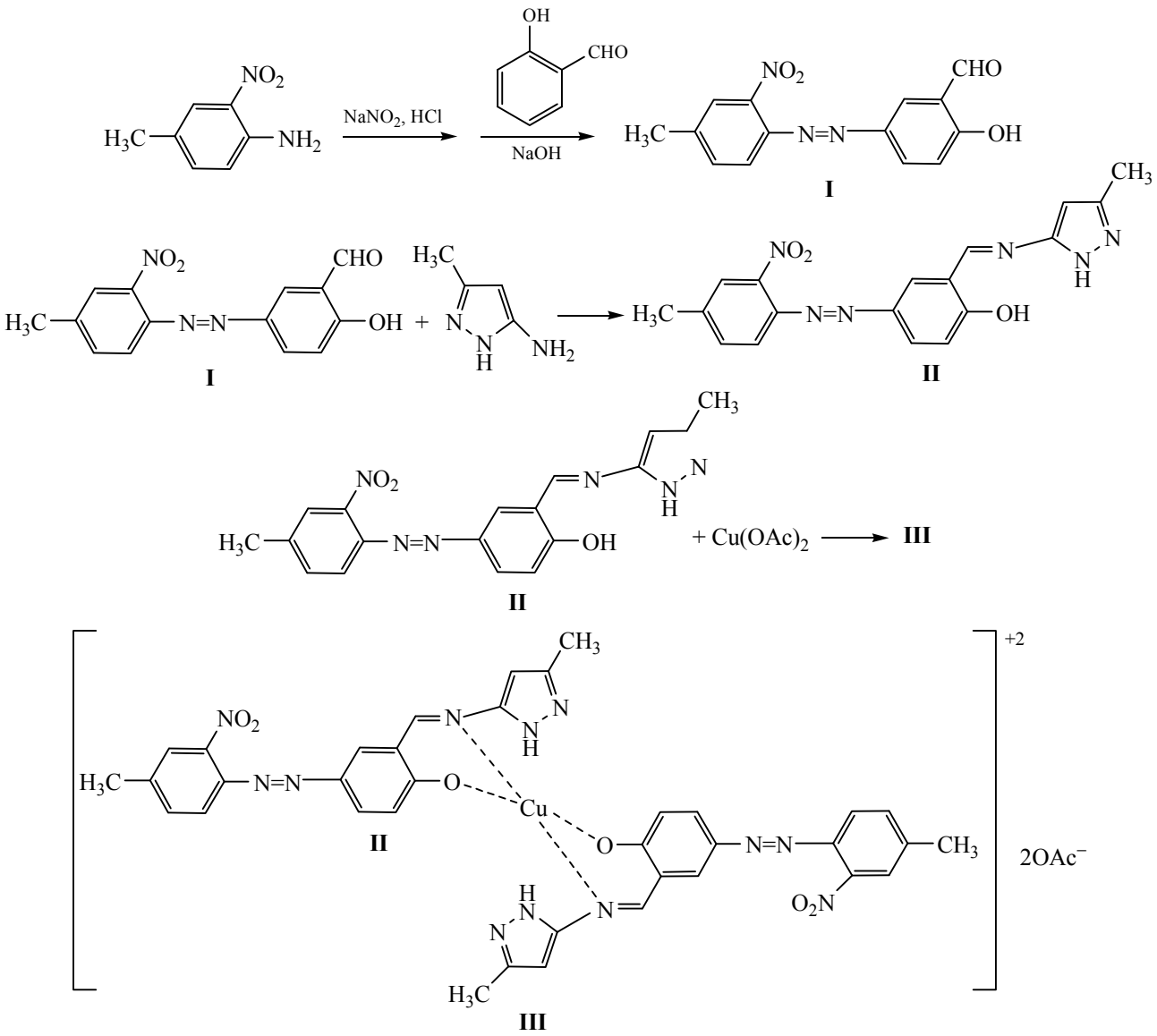

Fig. 1. Synthesis of complex **III**.

stopped, the complex was filtered to separate from the product. The crystalline products were obtained in high yields.

In continuation of our studies on the synthesis of heterocyclic and pharmaceutical compounds by mild and practical protocols [14, 15], herein we report on

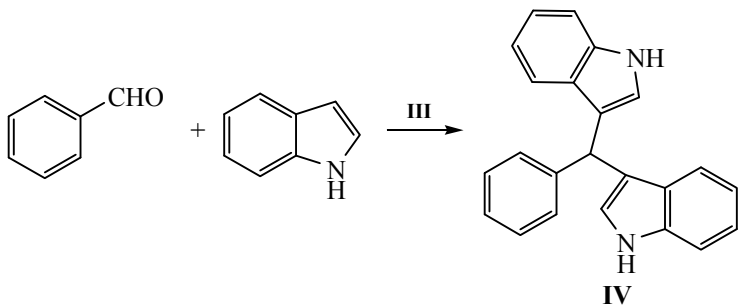

Fig. 2. Synthesis of diindolylmethanes using synthesized complex **III.**

Table 1. The effect of complex **III** amount on the synthesis of **IVa** under ultrasonic irradiation

Run no.	Catalyst amount (mmol) per 1 mmol of substrate	Time, min	Yield, %
1	–	450	–
2	0.025	60	66
3	0.050	5	92
4	0.100	5	93

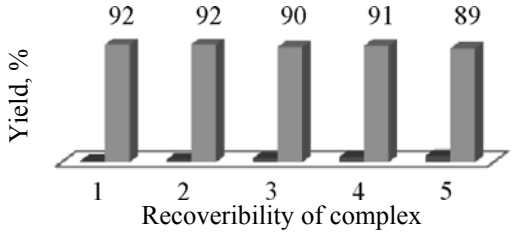

Fig. 3. Synthesis of **IVa**.

our experimental results on the synthesis of diindolylmethanes using different substituted aldehydes and indole derivatives in the presence of a new synthesized Schiff base's complex under ultrasound irradiation (Fig. 1).

Initially, a new Schiff base **II** was synthesized by refluxing azo-linked salicylaldehyde **I** with 5-methyl-3-aminopyrazole in EtOH. Then, we used this new Schiff base **II** for the preparation of our complex **III** by refluxing two equivalents of Schiff base **II** with $Cu(OAc)_2$ as described in Fig. 1.

In continuation of our studies, we applied the synthesized complex **III** as an effective and green catalyst to the condensation of benzaldehyde and indole under ultrasonic irradiation as a model reaction (Fig. 2).

We have studied the effect of catalyst amount on the model reaction and the results are listed in Table 1. 50 mg of complex is sufficient to promote the reaction to completion and 0.025 g of catalyst was not enough. Higher amounts of catalyst did not lead to significant change in the reaction yields. To generalize the procedure we have prepared a number of known and unknown diindolylmethanes following the ecofriendly methodology. The results are summarized in Table 2.

Apart from the mild condition of the process and its excellent results, the simplicity of product isolation, replacement of small amount of catalyst and the

Table 2. Synthesis of simple diindolylmethanes using new complex **III** under ultrasonic irradiation

Run no.	Aldehyde	Indole	Product	Time, min	Yield, %[a,b]	mp, °C
1	Benzaldehyde	indole	**IVa**	5 (120)[c]	92 (81)[c]	108–110
2	2-Cl-benzaldehyde	indole	**IVb**	8	89	76–77
3	3-Cl-benzaldehyde	indole	**IVc**	7	91	84–86
4	4-Cl-benzaldehyde	indole	**IVd**	5	95	78–80
5	2-NO_2-benzaldehyde	indole	**IVe**	9	92	111–112
6	3-NO_2-benzaldehyde	indole	**IVf**	5	95	265–266
7	4-NO_2-benzaldehyde	indole	**IVg**	3	98	235–237
8	4-OCH_3-benzaldehyde	indole	**IVh**	8	96	185–186
9	2-OH-benzaldehyde	indole	**IVi**	9	87	86–87
10	4-OH-benzaldehyde	indole	**IVj**	7	89	122–123
11	Indole-3-carbaldehyde	indole	**IVk**	5	97	161–163
12	Furfural	indole	**IVl**	6	95	308–309

[a] Isolated yield. [b] The products were characterized by comparison of their spectroscopic data with those of samples synthesized by published procedures. [c] Classical reaction was carried out using indol (2 mmol), benzaldehyde (1 mmol), and complex **III** in EtOH (10 mL) under reflux condition.

Table 3. Comparison of the newly developed procedure with the previously reported methods

Method number	catalyst	Amount of catalyst	Conditions	Time, min	Yield, %
1	Trichloro-1,3,5-triazine [4]	10%	rt	15	92
2	12-Tungstophosphoric acid supported on zirconia [9]	0.25 mol %	60°C	30	90
3	Zeolite [5]	0.5 g	rt	120	80
4	Zeokarb-225 [6]	0.5 g	rt	450	95
5	Oxalic acid [10]	10 mmol	80°C	40	96
6	Diphosphooctadecatungstic acid [11]	0.7 mol %	Solvent free, 110°C	40	96
7	Iodine [7]	0.2 mmol	rt, solvent free	10	72
8	Aminosulfonic acid [8]	1.5 mmol	Ultrasonic irradiation, 30–38°C	30	93
9	Aluminum oxide [12]	0.5 g	Microwave, 450W	5	97
10	Phosphated zirconia [13]	20 wt %	Solvent free	20	93
11	Present complex	0.05 g	Ultrasonic irradiation	5	92

possibility to recycle synthesized complex offer a significant advantage. After the reaction was completed, the catalyst could be easily filtered in hot EtOH to separate from product. After further treatment including washing with $CHCl_3$ and activation at 60°C, the recycled catalyst has been examined in the next run. Studies on the synthesis of **IVa** as model substrate showed that the recovered catalyst could be successively recycled in subsequent reactions without any decrease of yields (Fig. 3).

To investigate the efficiency of this method, the comparison between this procedure and some of previously reported reactions was carried out. The results are shown in Table 3, Figs. 5 and 4.

2-{(*E*)-[3-Methyl-1*H*-pyrazol-5-ylimino]methyl}-4-[(2-methyl-4-nitrophenyl) diazenyl]phenol (II). Yellow solid; mp: 215°C; ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 2.25 s (3H), 2.69 s (3H), 6.26 s (1H), 7.08 br (1H), 7.60 br (1H), 7.92 br (1H), 8.08 br (1H), 8.21 br (2H), 9.10 s (1H), 12.62 s (1H), 14.13 s (1H). ^{13}C NMR (125 MHz, DMSO-d_6), δ, ppm: 17.89, 23.50, 95.81, 117.29, 118.97, 120.12, 127.04, 127.65, 129.92, 130.01, 139.10, 141.07, 146.05, 148.51, 154.21, 155.12, 157.46, 161.72. IR (KBr), ν, cm^{-1}: 3274(OH), 3191, 2991, 1614 (CO), 1519 (NO_2), 1434, 1342 (NO_2), 1288. Calculated, %: C 59.35; H 4.82; N 23.49. $C_{18}H_{16}N_6O_3$. Found, %: C 59.43; H 4.76; N 23.55.

Complex II. Brown solid; mp: >300°C; Calculated, %: C 33.46; H 2.56; N 13.42. $C_{36}H_{32}Ac_2CuN_{12}O_8$. Found, %: C 33.38; H 2.70; N 13.51.

CONCLUSIONS

In conclusion, this protocol under ultrasonic irradiation provides a green, fast and practical method for the preparation of diindolylmethanes in short

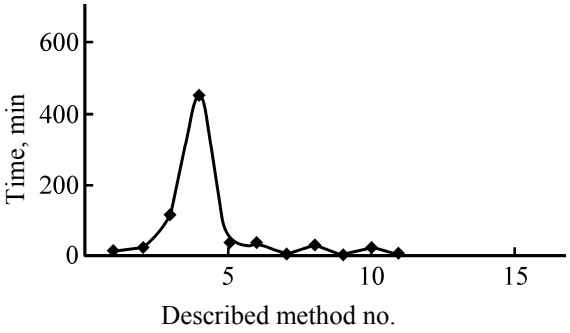

Fig. 4. Comparison of reaction time between the new method and reported methods in the case of benzaldehyde.

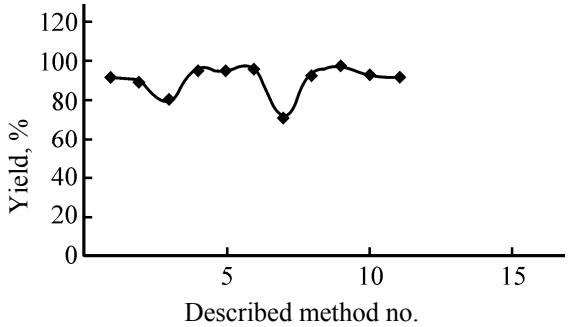

Fig. 5. Comparison of reaction yield between the new method and reported methods in the case of benzaldehyde.

reaction times and excellent yields. The simplicity, high atom economy, easy execution and work up, productivity, together with the use of inexpensive material and environmentally friendly procedure are the remarkable features of this process.

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