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Original Research Article

Cu(II)-Schiff base/SBA-15 as an efficient catalyst for synthesis of decahydroacridine-1,8-diones

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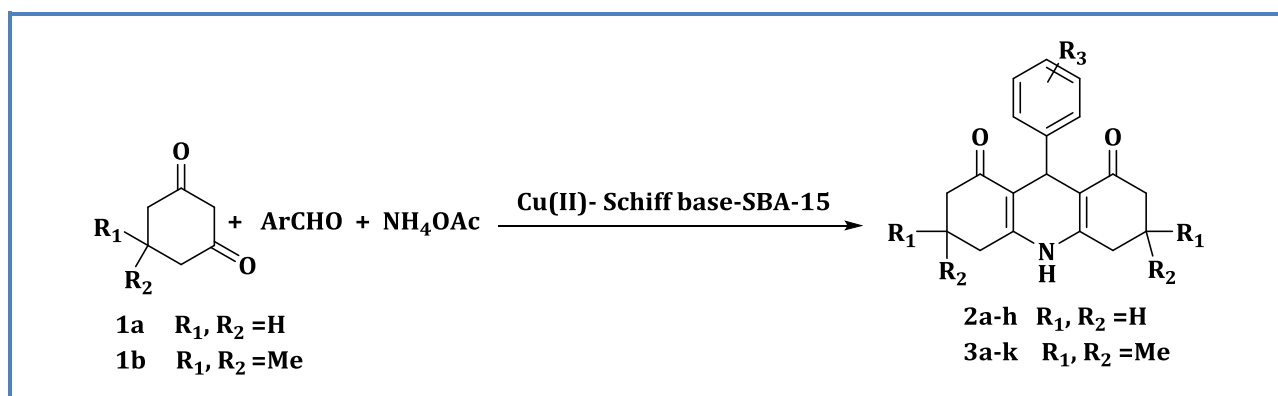
Cu(II)-Schiff base/SBA-15

Heterogeneous catalyst

ABSTRACT

Herein, we report a fast synthesis of 1,4-dihydropyridines, decahydroacridine-1,8-diones by one-pot multi-component reaction of 1,3-cyclohexanedione or dimidone, arylaldehydes, and ammonium acetate under solvent-less condition using Cu(II)-schiff base-SBA-15 as a reusable heterogeneous catalyst in high yields. These kinds of catalysts are built from mesoporous silica SBA-15 which was covalently anchored with Cu(II) schiff base complex. The shorter reaction times, good yields, simple work-up procedure and environmentally friendly conditions are the main advantages of this method compared to the last one. This method is also the first example of synthesizing acridines by Cu(II)-schiff base-SBA-15 as an efficient catalyst in solvent-free media which can be valuable to be used or investigated for similar systems. The product was identified by its ¹H NMR, mass and IR spectra, which were compared to those reported previously.

Graphical Abstract



Introduction

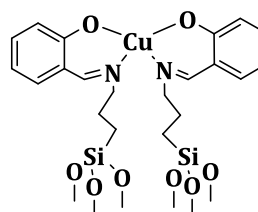
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4-Aryl-1,4-dihydropyridines (1,4-DHPs) have proved to be valuable as drugs for the treatment of cardiovascular disorders [1], and constitute an important class of calcium channel blockers [2, 3]. With a 1,4-DHP parent nucleus, decahydroacridine-1,8-diones have been shown to have very high lasing efficiencies [4] and used as photoinitiators [5]. Many acridinediones have been synthesized by the reactions of the aldehydes with 2 equivalent of 1,3-cyclohexanedione and appropriate amines in the presence of different catalysts such as $n\text{-TiO}_2$ [6], $[\text{MIMPS}]_3\text{PW}_{12}\text{O}_{40}$ and $[\text{TEAPS}]_3\text{PW}_{12}\text{O}_{40}$ [7], nano ZnO [8], and CAN [9]. Despite the potential utility of these methods published so far, they suffer from different limitations, such as difficulty in catalyst separation, difficulty in handling of catalyst, use of expensive catalysts, organic solvents, and also occurrence of side reactions. Therefore, the discovery of new and inexpensive catalysts for the preparation of 1,4-DHPs is of prime importance. As part of our continuing interest in the development of new synthetic methodologies [10], we report herein an efficient and convenient procedure for the synthesis of 1,4-DHPs in the presence of Cu(II)-schiff base/SBA-15 catalyst.

These kinds of catalysts are built from mesoporous silica SBA-15 which was covalently anchored with Cu(II) schiff base complex (Scheme 1) [11]. There are few literatures about the application of these kinds of catalysts (silica-supported schiff base cobalt (II) (Co/SBA-15) and copper (II) (Cu/SBA-15) complexes) for synthesis of heterocyclic compounds [12] specially for synthesis of acridines and our method is probably the first example of synthesizing acridines supported schiff base metal complexes as an efficient catalyst in solvent-free media which can be valuable to use or investigate for similar systems.

These reported examples have demonstrated that the new procedure by solid-supported catalysts are generally faster, give higher yields, and typically require easier work-up processes and simpler equipment than the extant methods.

Scheme 1. Structure of Cu(II)-schiff base/SBA-15



Experimental

Materials and methods

^1H NMR spectra were taken in CDCl_3 on a Bruker 500 MHz spectrometer (Bruker, Rheinstetten, Germany). The IR spectra were obtained in KBr disks on a Nicolet FT-IR magna 550 instrument

(Nicollet, Madison, WI, USA). Electron-impact mass spectra were then resulted using a Finnegan MAT TSQ-70 spectrometer (Finnegan Mat, Bremen, Germany). The purity of compounds was confirmed via thin layer chromatography (TLC) using different mobile phases.

Preparation of the catalyst Cu (II)-schiff base/SBA-15

The Cu(II)-schiff base complex was prepared using the pertinent literature procedure [11] with the following modification. Activated silica gel SBA-15 (1.5 g) was suspended in a methanol solution of the schiff base complex, and the mixture was stirred at the room temperature for 24 h. The solvent was then removed using a rotary evaporator, and the resulting green solid was dried at 80 °C overnight. The final product was washed with MeOH and deionized water until the washings were colorless to ensure that the noncovalently grafted complex and physically adsorbed metal species were removed. Further drying was carried out in an oven at 80 °C for 8 h. Moreover, in order to measure the amount of copper loaded into SBA-15, the catalyst (0.1 g) was digested with HNO₃ by stirring at room temperature for a week. Then the mixture was filtered, and the total amount of copper in SBA-15 in the colorless sample was determined as 0.14 mmol/g by atomic absorption spectroscopy.

General procedure for the synthesis of 9-aryl-3,4,6,7,9,10-hexahydroacridine-1,8 (2H,5H)-dione (**2a-h**)

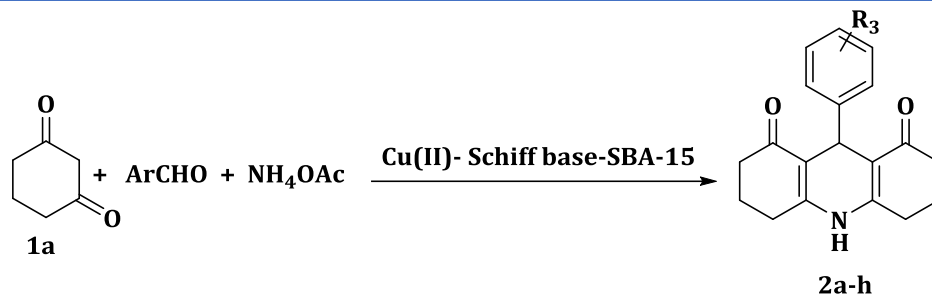
A combination of **1a** (2 mmol), ammonium acetate (0.23 g, 3 mmol), aryl aldehyde (1 mmol) and the catalyst (0.005 g, 0.007 mmol), were thoroughly mixed and placed in the autoclave at 112 °C for a certain time (Table 1). After cooling, the mixture was washed with EtOH (50 mL) and the catalyst was removed by filtration, rinsed twice with MeOH, and then dried at 80 °C for 60 min for subsequent reuse. Analytically, the pure products **2a-h** were obtained by evaporation of the solvent and recrystallization from EtOH. The yields and melting points are shown in Table 2. The products were identified by comparing with the original samples [6, 9].

General procedure for the synthesis of 3,3,6,6-tetramethyl-9-Aryl-3,4,6,7,9,10-hexahydroacridine-1,8 (2H,5H)-dione (**3a-k**)

A combination of **1b** (2 mmol), ammonium acetate (0.23 g, 3 mmol), aryl aldehyde (1 mmol) and the catalyst (0.005 g, 0.007 mmol), were thoroughly mixed and placed in the autoclave at 150 °C for a certain time (Table 2). After cooling, the mixture was washed with EtOH (50 mL) and the catalyst was removed by filtration, rinsed twice with MeOH, and then dried at 80 °C for 60 min for subsequent reuse. Analytically, the pure products **3a-k** were obtained by evaporation of the solvent

and recrystallization from EtOH. The yields and melting points are shown in Table 4. The products were identified by comparison with the original samples [6, 9].

Table 1. Synthesis of decahydroacridine-1,8-diones **2a-h** by Cu(II)-schiff base-SBA catalyst



Product ^a	R ₃	Yield (%) ^b	Time (min)	M.P. (°C)/ [Ref.]
2a	H	98, 97, 96, 96 ^c	8	278 (278-280) [6]
2b	4-Br	96.6	14	311 (310-312) [6]
2c	3-NO ₂	96	10	283 (282-284) [9]
2d	4-Cl	95	11	258 (258-259) [9]
2e	4-Me	91.6	11	254 (254-256) [6]
2f	2-OMe	83.3	15	301 (301-302) [9]
2g	4-OMe	91.6	14	303 (302-305) [6]
2h	2-OH	86.6	10	304 (302-304) [9]

^a All the products are known compounds and were characterized from their spectroscopic (¹H NMR and MS) properties

^b Isolated yield

^c Cu(II)-Schiff base-SBA was reused for four runs

Results and discussion

In our continued interest in the development of a highly expedient methodology [10, 13-15] for the synthesis of fine chemicals and heterocyclic compounds of biological importance, we report here the synthesis of decahydroacridine-1,8-diones, in the presence of Cu(II)-schiff base-SBA-15 as a reusable heterogeneous catalyst (Scheme 2).

We first studied a reaction between 1,3-cyclohexanedione and benzaldehyde and ammonium acetate by screening the reaction conditions (Table 3). In order to optimize the temperature, the reaction was carried out in different temperatures (Table 3, entries 1-3) and we found that the best yield and the highest rate was obtained in 112 °C (Entry 3). In the second step, the reaction was carried out with different amount of the catalyst (Table 3, entries 4-7) and the best result was obtained in the presence of Cu(II)(SBA-15) (0.005g, 0.007 mmol) at 112 °C. The less amount of the catalyst gave low yield even after a prolonged reaction time, and the more amounts could not cause obvious increase for the yield of the product and could not shorten the reaction time.

Finally, in order to show the role of the catalyst, the similar reactions were also examined in the presence of different catalysts such as Zr(II)(SBA-15), Pd(II)(SBA-15) and Fe(II)(SBA-15) in the same optimized conditions (0.005 g of catalyst in 112 °C) (Table 1, Entries 8-10 compared to entry 3). The best result was obtained with Cu(II)-schiff base-SBA-15 (Table 3, Entry 3).

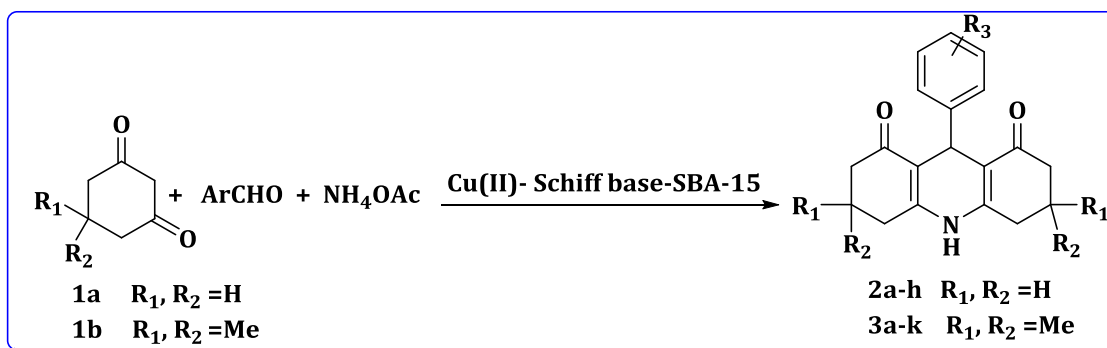
Table 2. Synthesis of decahydroacridine-1, 8-diones **3a-k** by Cu(II)-schiff base-SBA catalyst

Product ^a	R ₃	Yield (%) ^b	Time (min)	M.P. (°C)/ [Ref.]
3a	H	90	20	190 (190-191) [6]
3b	2-Br	75	16	>300 (>300) [16]
3c	4-Br	96.4	23	308 (308-310) [6]
3d	3-NO ₂	92	25	284 (284-285) [9]
3e	4- NO ₂	91	20	283 (283-285) [6]
3f	2-Cl	90	10	310 (310-312) [6]
3g	4-Cl	91	20	297 (297-299) [9]
3h	4-Me	92	15	268 (268-270) [9]
3i	2-OMe	95	20	293 (23-295) [9]
3j	4-OMe	85	12	300 (300-301) [6]
3k	2-OH	92	15	310 (310-312) [9]

^a All the products are known compounds and were characterized from their spectroscopic (¹H NMR and MS) properties

^b Isolated yield

After optimizing the conditions, we next examined the generality of these conditions to other substrates using several aromatic aldehydes (Scheme 2). The results are summarized in Table 1. It could be seen that Cu(II)-schiff base-SBA-15 as reusable heterogeneous catalyst catalyzed the condensation of 1,3-cyclohexanedione and a wide range of aromatic aldehydes at 112 °C. As indicated in Table 1, in all cases the reaction gives the products in good yields and prevents problems which many associate with solvent use such as cost, handling, safety and pollution.



Scheme 2. Synthesis of decahydroacridine-1,8-diones

Table 3. Optimization of the reaction condition for synthesis of decahydroacridine-1,8-diones

Entry ^a	R ₁	R ₂	R ₃	Temperature (°C)	Time (min)	Yield (%) ^b	Amount of Catalyst (g)	Type of catalyst
1	H	H	H	108	20	74.6	0.005	Cu(II)(SBA-15)
2	H	H	H	116	8	71.5	0.005	Cu(II)(SBA-15)
3	H	H	H	112	8	98	0.005	Cu(II)(SBA-15)
4	H	H	H	112	8	98	0.01	Cu(II)(SBA-15)
5	H	H	H	112	8	98	0.007	Cu(II)(SBA-15)
7	H	H	H	112	35	75	0.004	Cu(II)(SBA-15)
8	H	H	H	112	41	63.3	0.005	Zr(II)(SBA-15)
9	H	H	H	112	44	59.6	0.005	Pd(II)(SBA-15)
10	H	H	H	112	20	78.1	0.005	Fe(II)(SBA-15)
11	Me	Me	4-Chloro	115	34	48	0.005	Cu(II)(SBA-15)
12	Me	Me	4-Chloro	148	25	60	0.005	Cu(II)(SBA-15)
13	Me	Me	4-Chloro	150	20	91	0.005	Cu(II)(SBA-15)
14	Me	Me	4-Chloro	150	30	50	0.003	Cu(II)(SBA-15)
15	Me	Me	4-Chloro	150	20	91	0.005	Cu(II)(SBA-15)
16	Me	Me	4-Chloro	150	20	91	0.007	Cu(II)(SBA-15)

^a In all reaction the conditions were optimized for a 100% conversion

^b Isolated yield

^c The reaction was run under neat condition

To make this method more suitable we examined the reusability of the Cu(II)-schiff base/SBA-15, using 1,3-cyclohexanedione and benzaldehyde, as model substrates. For this aim after completion of the reaction (monitored by TLC), the catalyst was recovered by addition, ethanol and filtration, and dried at 80 °C for 60 min. The catalyst could be reused after washing twice with methanol and drying at 80 °C by vacuum evaporation. It could be seen that no considerable change in activity of Cu(II)-schiff base/SBA-15 was observed even after four consecutive runs (Table 1, entry 1).

In order to show the merit of the present method for the synthesis of decahydroacridine-1,8-diones, we have compared our results obtained using Cu(II)-schiff base/SBA-15 catalyst with some of those reported in the literature for the synthesis of 9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H, 5H)-diones **2a** (Table 4). These results indicate well the superior activity of Cu(II)-schiff base/SBA-15 catalyst than other catalysts.

Encouraged by these results, we carried out reaction of 5,5-dimethyl-1,3-cyclohexanedione **1b**, aromatic aldehydes, and ammonium acetate. Initially, the reaction of 5,5-dimethyl-1,3-cyclohexanedione **1b** with 4-chlorobenzaldehyde and ammonium acetate was selected as a model reaction in the presence of Cu(II)-schiff base-SBA-15 catalyst, in solvent-less condition. A series of experiments were performed to optimize catalyst loading and temperature (Table 3, entries 11-16). It could be seen that the best result was obtained with 0.005 g of Cu(II)-schiff base-SBA-15 at 150 °C (Table 3, entry 15).

With optimized reaction conditions in hand, 1,8-dioxo-decahydroacridine derivatives **3a-k** were synthesized in excellent yields within a short period of time in the optimized condition (Scheme 2, Table 2). Here also the aromatic aldehydes containing both electron-donating and electron-withdrawing groups afforded the products with high yields. The work-up procedure was so simple and including addition of ethanol at the end of the reaction, filtration, and finally recrystallizing the products from ethanol.

A plausible mechanism for the synthesis of decahydroacridine-1,8-diones **2a-h** and **3a-k** in the presence of the catalyst is shown in Scheme 3. Coordination of the carbonyl and nitrile groups in 1,3-cyclohexanedione and the intermediate **A** by the Cu²⁺ cation of the catalyst may increase electrophilicity of the carbonyl and nitrile groups in both condensation steps.

Table 4. Synthesis of 9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-diones **2a** using different catalysts

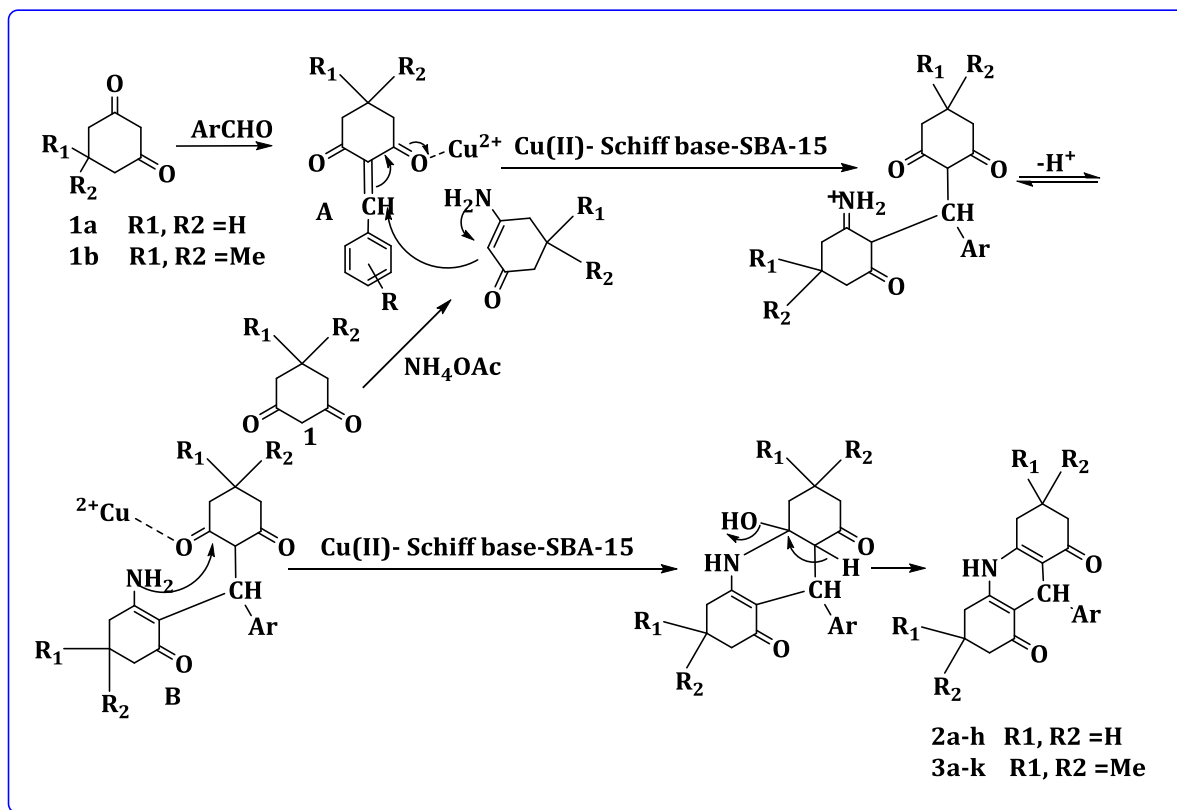
Entry	Catalyst	Solvent	Time (min)	Yield (%)	Ref.
1	Cu(II)- Schiff base-SBA-15	-	8	98	-
2	n-TiO ₂	EtOH	90	86	6
3	[MIMPS] ₃ PW ₁₂ O ₄₀	H ₂ O	36	91	7
4	[TEAPS] ₃ PW ₁₂ O ₄₀	H ₂ O	57	96	7
5	CAN	polyethylene glycol	15	98	9

^a Isolated yield

Conclusion

we have developed a novel and efficient method for the synthesis of 1,8-dioxo-decahydroacridines in high yields employing Cu(II)-Schiff base/SBA-15, as reusable heterogeneous

catalyst. The application of an inexpensive, easily available and reusable catalyst makes this method simple, clean, practical and economically viable. The method is an easy access to functionalized acridines.



Scheme 3. Plausible mechanism of the reaction

Acknowledgments

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