MCM-41-SO_3H as a Nanoreactor for the One-Pot, Solvent-Free Synthesis of 1,8-Dioxo-9-aryl Decahydroacridines

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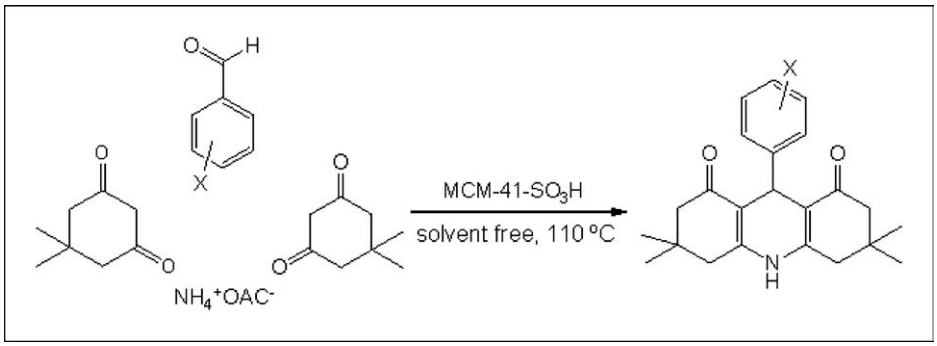

One-pot four-component synthesis of 1,8-dioxo-9-aryl decahydroacridines in solvent-free condition was efficiently performed in the presence of MCM-41-SO_3H as a nanocatalyst and nanoreactor in good yields. The method provides several advantages such as low cost, operational and experimental simplicity, high yields, and short reaction times.

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INTRODUCTION

1,8-Dioxo-9-aryl decahydroacridines and their derivatives are well-known polyfunctionalized 1,4-dihydropyridine derivatives that are widely prescribed as calcium channel blockers and used for the treatment of hypertension and defibrillation [1]. In addition, acridines are important compounds reported to have antitumor properties [2]. Reportedly, the conventional synthesis of 1,4-dihydropyridine derivatives was performed in organic solvents such as HOAc [3], CH_3CN [4], DMF [5], and water [6]. There has been considerable interest for further research toward simple procedure, low-catalyst loading, and using different substrates for the synthesis of 1,8-dioxo-9-aryl decahydroacridines.

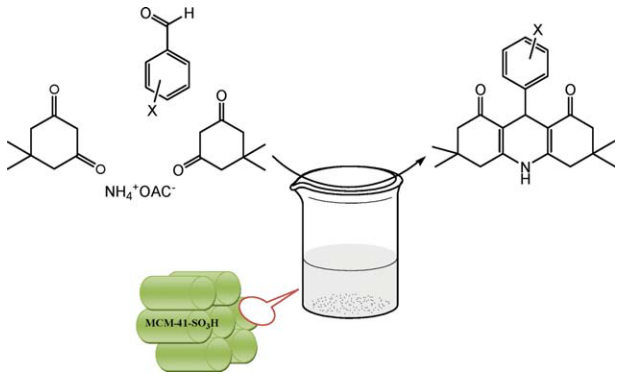
In recent years, more attractive possibilities have been arisen by the development of various new silica materials with ordered structure [7]. One of the best-known examples is MCM-41, which is a structurally well-ordered mesoporous material with a narrow pore size distribution between 1.5 and 10 nm, and a very high-surface area up to 1500 $m^2\ g^{-1}$ [8]. It has been proven that Si-MCM-41 lacks Brönsted acid sites and exhibits only weak hydrogen-bonding-type sites [9,10]. An additional possibility to develop acidic solids is the modification of the surface of suitable supporting materials, as the chemical functionalities of these materials can be uniformly modified by covalent anchoring of different organic moieties [11]. Although several types of solid sulfonic acids have been created in recent years, there have been only a few reports about their applications as catalyst in chemical transformations. Furthermore, to the best of our knowledge, there is no report on the use of these materials as nanocatalysts in the synthesis of 1,8-dioxo decahydroacridines.

In continuation of our work to develop new and eco-friendly synthetic methodologies toward different heterocyclic compounds [12], herein, we report a novel, green, facile, and an efficient one-pot method for the synthesis of 1,8-dioxo-9-aryl decahydroacridines derivatives from readily available starting materials, dimedone, ammonium acetate, and an aromatic aldehyde in the presence of MCM-41-SO_3H as a nanoctalyst under solvent-free conditions. (Scheme 1)

RESULTS AND DISCUSSION

Compared with known methods, our procedure is representing an expedient method for certain acridinedione derivatives with new application for a catalyst that has not been applied for this purpose till now. Additionally, the work covers today's basic trends in chemistry, such as environmentally benign systems and economical approaches with short workup procedures and higher yields.

Scheme 1. Four-component one-step synthesis of 1,8-dioxo-9-aryl decahydroacridines.



During our investigation, at first, we chose 4-chlorobenzaldehyde (1 mmol), dimedone (2 mmol), and ammonium acetate (3 mmol) under solvent-free conditions as model reactants and examined the effect of the amount of MCM-41-SO_3H, in which the optimum amount of catalyst was 0.005 g as shown in Table 1.

To evaluate the effect of solvent, we examined different solvents for the synthesis of 1,8-dioxo-9-aryl decahydroacridines in the presence of catalyst (Table 2). According to our findings, solvent-free conditions gave the best result for this transformation.

Subsequently, to optimize the reaction temperature, a mixture of 4-chlorobenzaldehyde (1 mmol), dimedone (2 mmol), ammonium acetate (3 mmol), and MCM-41-SO_3H (0.005 g) were mixed and heated in a paraffin bath at different temperature (Table 3). According to the data, the optimum temperature was selected as 110°C.

All of the reactions were carried out within 10–110 min and no by-product was observed by TLC analysis. The reaction worked well with electron-withdrawing (Cl, CN) as well as electron-donating (Me, MeO) groups, giving various acridine derivatives in 60–98% yields. As shown in Table 4, the method is general and includes a variety of functional groups.

It seems that at first the reaction of 1 mmol of dimedone with 1 mmol of an aldehyde as well as the reaction of 1 mmol dimedone with an ammonium acetate resulted in the formation of chalcone (**1**) and enamine (**2**) inside the nanocatalyst channels. Then, together with, the inherent Brönsted acidity of —SO_3H groups, which are capable of bonding with the carbonyl oxygen of the chalcone, generation of ionic intermediates is assisted by activation of the reactants. In other words, ionic intermediates are generated inside the nanoreactor by sufficient energy released during the collapse and strong polarity of the —SO_3H groups. Second, the Michael addition of the enamine to the chalcone leads to the formation of intermediate **(3)**. Finally, ring closure, together with water, elimination gives the product **(4)**. Therefore, under this reaction condition and by using this nanocatalyst, the reaction rates and yields are enhanced. (Scheme 2).

Table 1

Comparison of the amount of the catalyst and yields for the synthesis of **4k**.

Amount of catalyst (g)	Time (min)	Yield (%)
–	55	80
0.001	15	80
0.003	15	85
0.005	10	95

Table 2

The effect of the solvent for the synthesis of **4k** in the presence of 0.005-g catalyst.

Solvent	Time (min)	Yield (%)
EtOH (reflux)	140	85
CH_3CN (reflux)	130	70
H_2O (reflux)	195	79
Solvent free	10	98

CONCLUSION

In conclusion, we have used MCM-41-SO_3H as an effective nanocatalyst for the one-pot multicomponent synthesis of 1,8-dioxo-9-aryl decahydroacridine derivatives. This catalyst is highly efficient, easily available, economical, and requires mild reaction condition. The products were also formed in excellent yields with short reaction times. This method offers several advantages, such as omitting toxic solvents or catalyst, very simple work-up and needs no chromatographic method for purification of the products. The starting materials are also inexpensive and commercially available.

EXPERIMENTAL

General remarks. Melting points were recorded on a Buchi B-540 apparatus. IR spectra were recorded on an ABB Bomem Model FTLA200-100 instrument. ^1H NMR and ^{13}C NMR spectra were measured on a Bruker DRX-300 spectrometer, at 300 and 75 MHz, using TMS as an internal standard. Chemical shifts (δ) were reported relative to TMS, and coupling

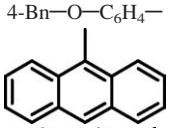
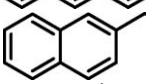
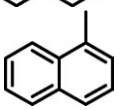
Table 3

The effect of reaction temperature for the synthesis of **4k** in the presence of 0.005-g catalyst.

Temperature (°C)	Time (min)	Yield (%)
80	35	82
90	25	86
100	25	90
110	10	98
116	15	98

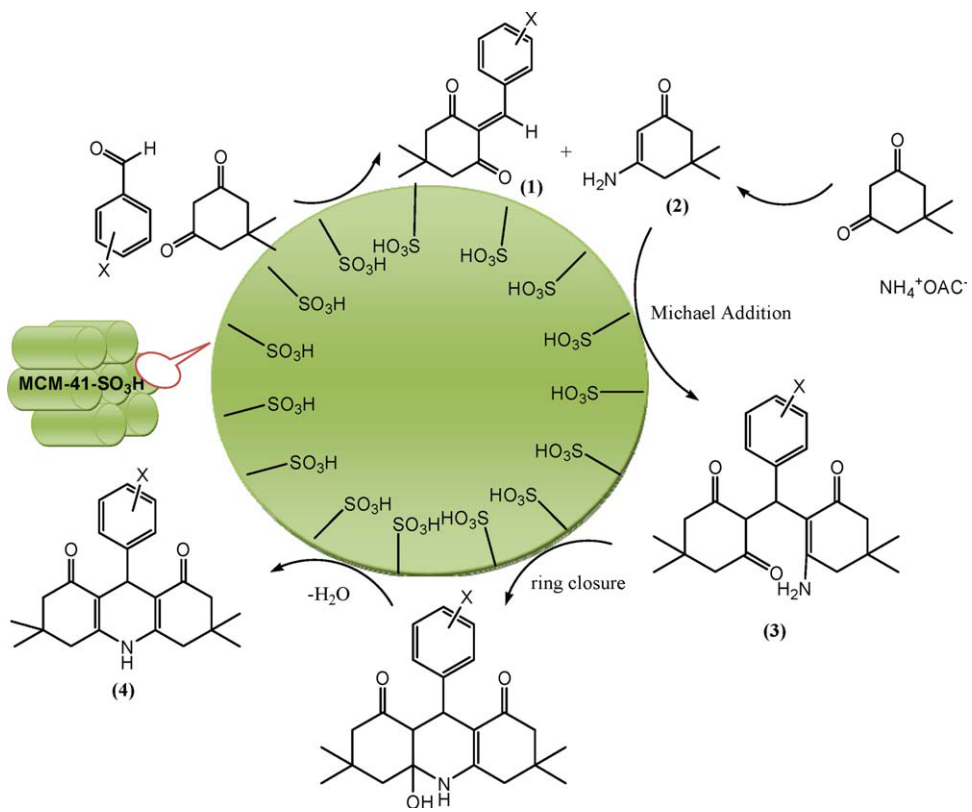
Table 4

The reaction time and the yield (%) of 1,8-dioxo-9-aryl decahydroacridines product.

Product	Ar	Time	Yield[a] (%)	M.P. (°C) found	M.P. (°C) reported
4a	2,3-Di-Cl_2—C_6H_4—	10	80	>323	–
4b	4-Acetamid—C_6H_4—	15	75	341–342	331–333 [14]
4c	4-CN—C_6H_4—	25	87	328–330	324–326 [14]
4d	4-Bn—O—C_6H_4—	15	94	165–167	–
4e		110	60	296–298	–
4f		20	98	>334	–
4g		20	97	305–307	–
4h	2,4-Di-Cl—C_6H_4	15	88	>321	>321 [15]
4j	2-Cl—C_6H_4—	10	96	309–310	231–233 [16]
4k	4-Cl—C_6H_4—	10	95	303–305	300–302 [17]
4l	4-Br—C_6H_4—	10	92	330–332	>300 [17]
4m	4-OCH_3—C_6H_4—	10	88	311–313	274–275 [3(b)]
4n	4-CH_3—C_6H_4—	20	88	332	>300 [18]
4o	3-OH—C_6H_4—	15	82	>302	>300 [19]
4p	4-OH—C_6H_4—	15	61	>304	>300 [18]

[a] Isolated yield.

Scheme 2. A provisional mechanisms for the synthesis of 1,8-dioxo-9-aryl decahydroacridines product.



constants (J) were reported in hertz (Hz). Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer with 70-eV ionization potential.

Synthesis and functionalization of MCM-41. In the present work, MCM-41 was modified to covalently anchor sulfonic acid on the inside surface of channels to provide the silica-supported material with Brönsted acid properties. The MCM-41 was synthesized according to the previously described method using cetyltrimethylammonium bromide (CTMABr), as the templating agent [13]. The surfactant template was then removed from the synthesized material by calcination at 540°C for 6 h.

MCM-41 was modified using a 100-mL suction flask equipped with a constant-pressure dropping funnel containing chlorosulfonic acid (81.13 g and 0.7 mol) and a gas inlet tube for conducting HCl gas over an adsorbing solution. Then, 60.0 g of MCM-41 was charged into it and chlorosulfonic acid was added dropwise over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately. After completion of addition, the mixture was shaken for 30 min, and the white solid (MCM-41-SO_3H) was obtained (115.9 g).

General procedure for the synthesis of 1,8-dioxo-9-aryl decahydroacridines. A mixture of aldehyde (1 mmol), dimedone (2 mmol), ammonium acetate (3 mmol), MCM-41-SO_3H (0.005 g) were mixed and heated in a paraffin bath at 110°C for different periods of time (Table 4). After completion of the reaction (monitored by TLC; petroleum ether and EtOAc, 1:2), excess ammonium acetate was washed away by water. Subsequently, products were crystallized from ethanol.

The spectral data of some representative products. ***3,3,6,6-Tetramethyl-9-(2,3-dichlorophenyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridin-1,8-dione (4a).*** Yellow solid, M.P. >322°C (KBr, cm^{-1}) V_{max}: 3286, 3178, 3049, 2957, 2859, 1647, ^{1}H NMR (300 MHz; DMSO-d_6): δ = 0.84 (6H, s, $2CH_3$), 0.99 (6H, s, $2CH_3$), 1.92 (2H, d, J = 16.0 Hz, 2CH), 0.14 (2H, d, J = 16.1 Hz, 2CH), 2.28 (2H, d, J = 17 Hz, 2CH), 2.45 (2H, d, J = 17 Hz, 2CH), 5.14 (1H, s, 1CH), 7.13–7.31 (3H, m, CH), 9.37 (1H, s, NH),^{13}C NMR (75 MHz, DMSO-d_6): 26.35, 29.01, 31.95, 33.67, 40.16, 50.16, 110.87, 126.98, 127.56, 129.05, 130.54, 131.41, 147.18, 149.78, 194.17. MS (EI): m/e = 417 (4) [M+], 382 (43), 272 (100), 256 (2), 216 (6), 188 (8), 160 (3), 144 (3), 109 (2), 83 (6), 77 (5), 55 (6).

N-(4-(1,2,3,4,5,6,7,8,9,10-Decahydro-3,3,6,6-tetramethyl-1,8-dioxoacridin-9yl)phenyl)acetamide (4b). Yellow solid, M.P. 341–342°C, (KBr, cm^{-1}) V_{max}: 3471, 3306, 3038, 2951, 1615, ^{1}H NMR (300 MHz; $CDCl_3$): δ = 0.85 (6H, s, $2CH_3$), 0.99 (6H, s, $2CH_3$), 1.99 (3H, s, CH_3), 1.94–2.49 (8H, m, $4CH_2$), 4.74 (1H, s, CH), 7.04 (2H, d, J = 8.48 Hz, 2CH), 7.31 (2H, d, J = 8.4 Hz, 2CH), 9.23(1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): 23.82, 25.44, 29.07, 32.10, 32.2, 38.66, 39.22, 39.50, 39.78, 40.05, 50.25, 11.50, 118.52, 127.88, 136.72, 142.08, 149.11, 167.88, 194.34 MS (EI): m/e = 406 (8) [M+], 405 (5), 377 (5), 272 (100), 102 (12), 43 (29).

3,3,6,6-Tetramethyl-9-(4-cyanophenyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridin-1,8-dione(4c). Yellow solid, M.P. 328–330°C , (KBr, cm^{-1}) V_{max}:3327, 3234, 3080, 2957, 2233, 1642, ^{1}H NMR (300 MHz; $CDCl_3$): δ = 0.84 (6H, s, $2CH_3$), 0.99 (6H, s, $2CH_3$), 1.98 (2H, d, J = 16 Hz, 2CH), 2.17 (2H, d, J = 16 Hz, 2CH), 2.33 (2H, d, J = 17 Hz, 2CH), 2.45 (2H, d, J = 17 Hz, 2CH), 4.85 (1H, s, CH), 7.33 (2H, d, J = 8.2 Hz, 2CH), 7.63 (2H, d, J = 18 Hz, 2CH), 9.40 (1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): 26.44, 28.93, 32.08, 33.82, 38.66, 39.21, 39.77, 40.05, 50.04, 105.27, 110.44, 118.94, 128.67, 131.53, 149.87, 152.40, 194.28 MS (EI): m/e = 374 (9) [M+], 273 (25), 272 (100), 271 (40), 140 (17), 102 (15), 83 (27).

3,3,6,6-Tetramethyl-9-(4-(benzyloxy)phenyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridin-1,8-dione (4d). Yellow solid, M.P.165–167°C, (KBr, cm^{-1}) V_{max}: 3604, 3352, 3286, 3029, 2952, 2859, 1611, ^{1}H NMR (300 MHz; $CDCl_3$): δ = 0.83 (6H, s, $2CH_3$), 0.95 (6H, s, $2CH_3$), 2–2.30 (8H, m, $4CH_2$), 4.85(2H, s, CH_2), 4.85 (2H, s, CH_2), 5.06 (1H, s, CH), 6.80 (2H, d, J = 8.63 Hz, 2CH), 7.26 (2H, d, J = 8.65 Hz, 2CH), 7.31 (5H, m, 5CH), 8.30 (1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): 27.07, 29.52, 32.54, 32.69, 40.48, 50.87, 69.84, 113.15, 114.09, 127.67, 127.87, 128.46, 128.91, 136.97, 139.41, 149.44, 156.98, 196.18 MS (EI): m/e = 455 (48) [M+], 364 (12), 272 (100), 91 (83), 65(17).

3,3,6,6-Tetramethyl-9-(anthracen-9-yl)-1,2,3,4,5,6,7,8,9,10-decahydroacridin-1,8-dione (4e). Yellow solid, M.P = 296–298°C (KBr, cm^{-1}) V_{max}: 3346, 3044, 2952, 1649, 1596, ^{1}H NMR (300 MHz; DMSO-d_6): δ = 0.66 (6H, s, $2CH_3$), 0.97 (6H, s, $2CH_3$),1.73 (2H, d, J = 16.3 Hz, 2CH), 2.05 (2H, d, J = 16.3 Hz, 2CH), 2.33 (2H, d, J = 16.9 Hz, 2CH), 2.51 (2H, d, J = 16.9 Hz, 2CH), 6.42 (1H, s, 1CH), 7.33 (2H, m, 2CH), 7.48 (2H, m, 2CH), 7.96 (2H, m, CH), 8.26 (1H, d, J = 8.6 Hz, CH), 8.34 (1H, s, 1CH), 9.11 (1H, d, J = 8.6 Hz, CH), 9.59 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 26.28, 29.12, 30.02, 31.56, 40.38, 50.23, 112.72, 124.00, 124.73, 126.25, 131.19, 139.73, 148.89, 194.46, MS (EI): m/e = 449 (24), 432 (4) [M+], 365 (2), 272 (71), 215 (36), 178 (100).

3,3,6,6-Tetramethyl-9-(naphthalen-2-yl)-1,2,3,4,5,6,7,8,9,10-decahydroacridin-1,8-dione (4f). Yellow solid, M.P > 334°C (KBr, cm^{-1}) V_{max}: 3291, 3173, 3044, 2952, 2854, 1647, ^{1}H NMR (300 MHz; DMSO-d_6): δ = 0.84 (6H, s, $2CH_3$), 1.00 (6H, s, $2CH_3$), 1.96 (2H, d, J = 16.1 Hz, 2CH), 2.18 (2H, d, J = 16.1 Hz, 2CH), 2.35 (2H, d, J = 17 Hz, 2CH), 2.48 (2H, d, J = 16.8 Hz, 2CH), 5.54 (1H, s, CH), 7.36–7.43 (3H, m, 3CH), 7.59 (1H, s, 1CH), 7.69–7.77 (3H, m, 3CH), 9.35 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 26.38, 29.13, 32.14, 33.28, 40.35, 50.24, 111.28, 125.06, 125.57, 125.70, 126.83, 127.09, 127.22, 127.54, 131.53, 132.72, 144.57, 149.46, 194.43 MS (EI): m/e = 399 (24) [M+], 382 (6), 314 (3), 272 (100), 256 (5), 216 (6), 188 (8), 127 (12), 77 (5).

3,3,6,6-Tetramethyl-9-(naphthalen-1-yl)-1,2,3,4,5,6,7,8,9,10-decahydroacridin-1,8-dione (4g). Yellow solid, M.P. 305–307°C, (KBr, cm^{-1}) V_{max}:3512, 3301, 3203, 3065, 2962, 2870, 1653, 1622, 1478 ^{1}H NMR (300 MHz; $CDCl_3$): δ = 0.81 (6H, S, $2CH_3$),1.00 (6H, s, $2CH_3$), 1.86 (2H, d, J = 16.2 Hz, 2CH), 2.14 (2H, d, J = 16.1 Hz, 2CH), 2.35 (2H, d, J = 17.04 Hz, 2CH), 2.51 (2H, d, J = 16.7 Hz, 2CH), 5.5 (1H, s, CH),7.2 (1H, d, J = 8.2 Hz, 1CH), 7.4 (1H, d, J = 7.3 Hz, 1CH), 7.5 (1H, d, J = 7.6 Hz, 1CH),7.6 (1H, d, J = 7.7 Hz, 1CH),7.8 (1H, d, J = 8.0 Hz, 1CH), 8.7(1H, d, J = 8.5 Hz, 1CH), 9.3 (1H, s, NH).^{13}C NMR (75 MHz, DMSO-d_6):18.55, 26.26, 29.15, 32.05, 50.18, 56.01, 113.16, 124.82, 125.34, 125.97, 126.12, 127.46, 132.76, 148.86, 194.47, MS (EI): m/e = 399 (140), 382 (2), 314 (4), 272 (100), 127 (42), 77 (16), 41 (23).

3,3,6,6-Tetramethyl-9-(2-chlorophenyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridin-1,8-dione(4j). Yellow solid, M.P. 309–310°C (KBr, cm^{-1}) V_{max}: 3286, 3198, 3055, 2957, 2859,1647, 1617 ^{1}H NMR (300 MHz; DMSO-d_6): δ = 0.86 (6H, s, $2CH_3$), 0.89 (6H, s, $2CH_3$), 1.99 (2H, d, J = 9.55 Hz, 2CH), 2.17 (2H, d, J = 8.07 Hz, 2CH), 2.33 (2H, d, J = 7.03 Hz,

2CH), 2.45 (2H, d, J = 8.54 Hz, 2CH), 4.77 (1H, s, CH), 7.12–7.29 (4H, m, 4CH), 9.34 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 25.35, 29.00, 32.11, 33.04, 50.10, 110.80, 120.88, 126.55, 128.31, 129.88, 130.45, 149.63, and 194.33.

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