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One-pot Synthesis of Benzo[*c*]acridine Derivatives Using SBA-Pr-SO_3H as Nano Catalyst

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Abstract. One-pot synthesis of benzo[*c*]acridine derivatives via the three-component condensation reaction of aromatic aldehydes, 1-naphtylamine, and dimedone using sulfonic acid functionalized SBA-15 (SBA-Pr-SO_3H) as nanoporous acid catalyst under solvent-free conditions was studied. This reaction is an efficient, green and environmentally friendly procedure.
Key words: Sulfonic acid functionalized SBA-15, benzoacridine, one-pot synthesis, dimedone, 1-naphthylamine.

Resumen. Se estudió la síntesis de derivados de benzo[*c*]acridina mediante la condensación de tres componentes en un solo paso, de aldehídos aromáticos, 1-naftilamina y dimedona, empleando como catalizador el ácido sulfónico SBA-15 (SBA-Pr-SO_3H) en condiciones libres de disolvente. Esta reacción es un método eficiente, verde y amigable al medio ambiente.
Palabras clave: Ácido sulfónico funcionalizado SBA-15, benzoacridina, síntesis en un solo paso, dimedona, 1-naftilamina.

Introduction

Acridine derivatives have a wide spectrum of biological activities such as antibacterial [1], cytotoxic [2], antifungal [3] and anti-malarial [4] activities. For example Amsacrine (Fig. 1) is an antineoplastic agent [5]. The synthesis of new polycyclic acridine skeletons fused with a five or six-membered rings, have been extensively studied because they play important roles in some DNA-intercalating anticancer drugs [6-7]. Benzo[*c*]acridine derivatives have been recently synthesized by a number of methods via one-pot multi-component condensation reactions of naphthylamines, dimedone and aldehydes in different conditions, for example, using triethylbenzylammonium chloride (TEBAC)/H_2O [8], ionic liquid [9], under microwave irradiation (MWI) [10-12], or ultrasound irradiation (USI) [13].

In recent years, the one-pot multi-component reactions have received significant attention because two or more steps in the synthetic sequence can be carried out without the isolation of intermediates which leads to reduction of time and energy for developing new pharmaceutically important compounds [14]. Recently, our research group has developed various multi-component reactions which can provide easy access to useful functionalized multiple ring structures of chemical and pharmaceutical interest [15-20].

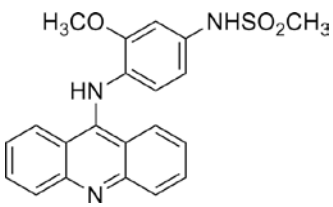


Fig. 1. Amsacrine Structure.

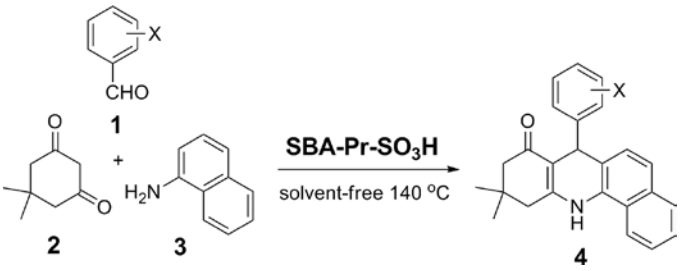
Use of heterogeneous catalysts has recently received considerable interest in various organic synthesizes. The SBA-15 is a nanoporous silica which has a hexagonal structure, large pore size, high surface area and high thermal stability. Among mesoporous silica materials SBA-15 is more diffusion free because of its thicker pore walls and larger pore size [21]. There are only a few reports in the application of SBA-Pr-SO_3H as nano acid catalyst in chemical transformations [22-25].

By considering the above reports, the development of novel and simple methods for the efficient preparation of polycyclic acridines containing naphthalene and quinolones fragments will be therefore an interesting challenge. In continuation of our previous works on the application of heterogeneous solid catalysts in organic synthesis [15-20, 26], herein, we would like to report a highly efficient method for the synthesis of benzo[*c*]acridine derivatives using SBA-Pr-SO_3H under solvent-free conditions.

Results and Discussion

The synthesis of 7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-one derivatives **4** were achieved via the three component condensation reaction of aromatic aldehydes **1**, dimedone **2**, and 1-naphthylamine **3** using SBA-Pr-SO_3H as a highly active nanoporous heterogeneous acid catalyst (Scheme 1).

We first studied a reaction between 4-chlorobenzaldehyde, dimedone and 1-naphthylamine in the presence of SBA-Pr-SO_3H for the screen of reaction conditions. For optimization of reaction conditions, we examined the influence of different solvents and the reaction times as shown results in Table 1. Among the tested solvents such as H_2O, EtOH, EtOH/H_2O (1:1), CH_3CN, and solvent-free system, the best result was obtained after 5 min in solvent-free conditions in excellent yield.



Scheme 1. Synthesis of 7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-one derivatives **4** in the presence of SBA-Pr-SO_3H.

In order to determine the influence of SBA-Pr-SO_3H for synthesis of benzo[*c*]acridine derivatives we next examined the above reaction in the presence of different catalysts at 140 °C in solvent-free conditions. As shown in Table 2, the best results were also obtained in the presence of SBA-Pr-SO_3H as catalyst.

After optimizing the reaction conditions, we next developed the solvent-free conditions at 140 °C to the synthesis of other derivatives using several aromatic aldehydes as shown results in Table 3. By these conditions, the reactions were carried out easily to produce benzo[*c*]acridine derivatives in good yields and no undesirable by-products were observed. This protocol offers advantages in terms of its simple procedure and work-up, use of the green and reusable catalyst, and excellent yields. The experimental procedure is very simple, convenient and has the ability to tolerate a variety of other functional groups such as methyl, methoxy, nitro, hydroxyl and halides under the reaction conditions. It was indicated that both electron-rich and electron-deficient aldehydes worked well, mostly leading to high yields of products. For all substrates, the reaction could be completed in 2-13 min with high yields. After completion of the reaction (monitored by TLC), the crude product was dissolved in hot ethanol, the heterogeneous solid catalyst was removed easily by simple filtration, and after cooling of the filtrate, crystals of pure products were obtained. The acid catalyst can be recycled by simple washing subsequently with diluted acid solution, water and acetone, and then reused without noticeable loss of reactivity. As shown in Table 4, the recovered SBA-Pr-SO_3H could be recycled for five times without any significant loss of reactivity. The new products were characterized by melting points, ^1H NMR, ^{13}C NMR and IR spectroscopic analyses. Melting points are compared with reported values in literature as shown in Table 3.

In these processes, SBA-Pr-SO_3H plays an important role in the accelerating of reaction. A suggested mechanism for this transformation is proposed in Scheme 2. SBA-Pr-SO_3H acts as a source of H^+, which can protonate the carbonyl group to create a more reactive species. In this reaction, an intermediate is formed through the Knoevenagel reaction between dimedone and aldehyde, and subsequently, by dehydration, olefin **5** is produced. Subsequent Michael-type addition of 1-naphthylamine

Table 1. The optimization of reaction conditions for the synthesis of **4a**.

Entry	Solvent	Conditions	Time (h)	Yield (%)
1	H_2O	Reflux	4	77
2	EtOH	Reflux	3	86
3	EtOH/H_2O (1:1)	78 °C	3	67
4	CH_3CN	Reflux	3	85
5	Neat	140 °C	5 min	96

Table 2. Synthesis of **4a** in the presence of different catalysts at 140 °C.

Entry	Catalyst	Time (min)	Yield (%)
1	—	30	45
2	Molecular sieve 4A	20	62
3	NH_2SO_3H	100	70 [27][a]
4	SBA	20	58
5	SBA-Pr-SO_3H	5	96

[a] The reaction was carried at 120 °C.

Table 3. SBA-Pr-SO_3H catalyzed synthesis of benzo[*c*]acridine derivatives **4** under solvent-free conditions.

Entry	Aldehyde	Product	Time (min)	Yield%	mp (°C)	mp (°C)[Lit]
1	4-ClC_6H_4	**4a**	5	96	268-270	268-270 [13]
2	3-$NO_2C_6H_4$	**4b**	2	90	254-257	267-269 [8]
3	4-OHC_6H_4	**4c**	6	88	281-283	280-282 [11]
4	2,4-$Cl_2C_6H_3$	**4d**	4	83	287-289	285-287 [13]
5	2,3-$Cl_2C_6H_3$	**4e**	10	92	288-290	—
6	C_6H_5	**4f**	13	83	256-258	258-259 [9]
7	4-$NO_2C_6H_4$	**4g**	10	90	283-285	281-283 [28]
8	2-$OCH_3C_6H_4$	**4h**	5	85	262-264	267-269 [13]
9	4-$(CH_3)_2NC_6H_4$	**4i**	10	83	265-268	276-278 [8]
10	3-OH-4-$OCH_3C_6H_3$	**4j**	10	88	252-254	—
11	4-$OCH_3C_6H_4$	**4k**	2	84	245-249	257-259 [12]
12	2-OHC_6H_4	**4l**	5	83	218-220	218-220 [13]

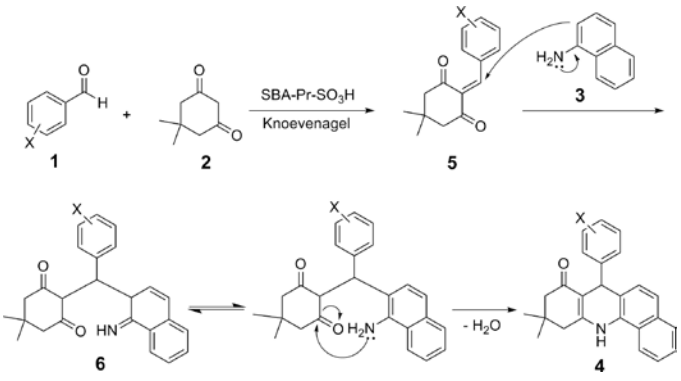
Table 4. Synthesis of benzo[*c*]acridine derivative **4a** with recycled SBA-Pr-SO_3H.

	1st run	2nd run	3rd run	4th run	5th run
Time (min)	5	5	6	7	7
Yield (%)[a]	96	93	94	92	90

[a] Recycle experiments were carried out on 1 mmol reaction of 4-chlorobenzaldehyde, dimedone and 1-naphthylamine in the presence of SBA-Pr-SO_3H at 140 °C. After each run, the recovered catalyst can be reactivated by simple washing subsequently with diluted acid solution, water and acetone.

3 to the olefin **5** produces **6**, which tautomerizes and cyclized to the corresponding products **4 (a-l)**.

The high yields of reactions are attributed to the effect of nano pore size about 6 nm of solid acid catalyst, which could act as nano-reactor (Fig. 2). This figure also illustrates the SEM and TEM images of SBA-Pr-SO_3H. SEM image (Fig. 2 left) shows uniform particles about 1μm. The same morphology was observed for SBA-15. It can be concluded that morphology of solid was saved without change during the surface modifications. On the other hand, the TEM image (Fig. 2 right) reveals the parallel channels, which resemble the pores configuration of SBA-15. This indicates that the pore of SBA-Pr-SO_3H was not collapsed during two steps reactions.



Scheme 2. Proposed mechanism for the synthesis of benzo[*c*]acridine derivatives **4**.

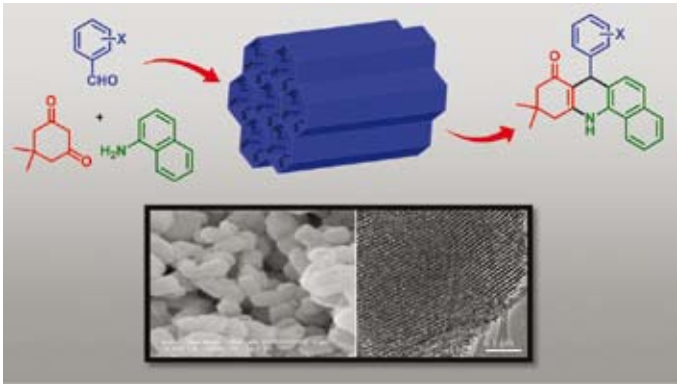


Fig. 2. SBA-Pr-SO_3H acts as a nano-reactor.

The nanoporous compound SBA-15 was prepared according to our previous report and its functionalization was effected as demonstrated in Fig. 3 [19].

The synthesis of benzo[*c*]acridine derivatives have been studied under several conditions in literature, as shown in Table 5. In contrast with other existing methods, the present methodology offers several advantages such as excellent yields, simple procedure, short reaction times, easy synthesis, simple work-up and greener conditions.

Conclusions

In conclusion, we demonstrated that SBA-15-Pr-SO_3H is an active nanoreactor catalyst in the synthesis of benzo[*c*]acridine derivatives. It could be recovered and reused for several reaction cycles without considerable loss of reactivity. Furthermore, the reasonable reaction times, excellent yields, simple work-up procedure, and environmentally friendly conditions are particular merits of this method. Further investigations into the scope and synthetic applications of this nano catalyst are currently under investigation in our laboratory.

Experimental Section

IR spectra were recorded from KBr disk using a FT-IR Bruker Tensor 27 instrument. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were run on a Bruker DPX spectrometer. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

General Procedure for the synthesis of 7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-ones

The sulfonic acid functionalized SBA-15 (0.02 g) was activated in vacuum at 100 °C and then after cooling to room temperature, 5,5-dimethylcyclohexane-1,3-dione **1** (2 mmol, 0.28 g), aromatic aldehyde **2** (2 mmol), and 1-naphthylamine **3** (2 mmol, 0.28 g) were added to it. The mixture was heated at 140 °C in solvent free conditions for an appropriate time as shown in Table 3. The reaction was monitored by TLC. After the completion of the reaction, the mixture was dissolved in hot ethanol in order to separate catalyst and then the filtrate was cooled to afford the pure product. The catalyst was washed subsequently with diluted acid solution, distilled water and then acetone, dried under vacuum and recycled for several times without loss of significant activity. The spectral (^{1}H NMR, ^{13}C NMR, MS, elemental analysis and IR) data for new compounds are given below.

10,10-Dimethyl-7-(2,3-dichlorophenyl)-7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-one (4e). Amorphous powder: mp 288-290 °C, IR (KBr) υ_{max} 3351, 3091, 2952, 17041, 1648,

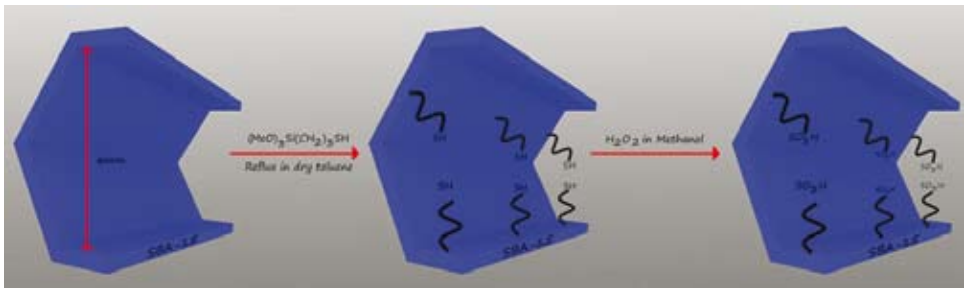


Fig. 3. Preparation of SBA-Pr-SO_3H.

Table 5. Comparison of different conditions in the synthesis of benzo[*c*]acridine derivatives **4**.

Entry	Catalyst	Solvent	Condition	Time	Yield (%)	Year	Ref.
1	TEBAC	H_2O	Reflux	12-18 h	85-98	2006	[8]
2	—	EtOH	USI	1-1.5 h	81-91	2010	[13]
3	BNBTS	—	90 ˚C	5-83 min	82-96	2010	[29]
4	—	—	~120-140 ˚C	1-5 min	82-87	2009	[30]
5	—	EtOH	MWI (220 W)	6-19 min	75-98	2006	[12]
	6	SBA-Pr-SO_3H	—	140 ˚C	2-13 min	83-96	This work

TEBAC: Triethylbenzylammonium chloride
BNBTS: *N,N'*-dibromo-*N,N'*-1,2-ethanediyl*bis*(*p*-toluenesulfonamide)

1528, 1484, 1430, 1348, 1220, 1125, 1052, 825, 785 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 9.28 (1H, s, NH), 7.06-8.06 (9H, m, ArH), 5.79 (1H, s, CH), 2.64-2.90 (2H, m, CH_2), 2.21 (1H, d, J = 16.8 Hz, CH_2), 2.03 (1H, d, J = 16.8 Hz, CH_2), 1.06 (3H, s, CH_3), 1.00 (3H, s, CH_3); ^{13}C NMR (DMSO-d6, 100 MHz): δ 193.51, 152.54, 148.98, 132.59, 131.66, 130.32, 129.00, 128.71, 128.35, 128.28, 128.12, 126.61, 126.13, 126.10, 123.17, 122.24, 121.45, 119.95, 106.84, 50.11, 38.34, 32.22, 29.26, 26.92; EIMS *m/z* (rel. int.): 421 $[M]^+$ (25), 386 (20), 276 (28), 143 (45), 57 (100); Anal. calcd. for $C_{25}H_{21}Cl_2NO$: C, 71.10; H, 5.01; N, 3.32%. Found: C, 71.13; H, 5.04; N, 3.28%.

10,10-Dimethyl-7-(3-hydroxy-4-methoxyphenyl)-7,10,11,12-tetrahydrobenzo[*c*]acridin-8(9*H*)-one (4j). Amorphous powder: mp 252-254 °C, IR (KBr) υ_{max} 3220, 2957, 1697, 1643, 1588, 1565, 1527, 1460, 1370, 1274, 1244, 1225, 1149, 1128, 777 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 13.36 (1H, s, OH), 9.26 (1H, s, NH), 8.46 (1H, d, J = 7.8 Hz, ArH), 7.80 (1H, d, J = 7.8 Hz, ArH), 7.43-7.56 (7H, m, ArH), 5.22 (1H, s, CH), 3.75 (3H, s, CH_3O), 2.71 (1H, d, J = 16.8 Hz, CH_2), 2.63 (1H, d, J = 16.8 Hz, CH_2), 2.22 (1H, d, J = 16.8 Hz, CH_2), 2.03 (1H, d, J = 16.8 Hz, CH_2), 1.06 (3H, s, CH_3), 0.96 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 193.68, 151.50, 146.03, 145.76, 141.64, 132.32, 130.48, 128.26, 128.03, 125.79, 125.68, 122.63, 122.20, 121.34, 121.27, 117.74, 114.66, 111.91, 107.54, 55.60, 50.37, 40.35, 32.17, 29.43, 26.87; EIMS *m/z* (rel. int.): 399 $[M]^+$ (5), 325 (65), 265 (100), 209 (70), 180 (90); Anal. calcd. for $C_{26}H_{25}NO_3$: C, 78.17; H, 6.31; N, 3.51%. Found: C, 78.20; H, 6.29; N, 3.48%.

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