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An Efficient One-Pot Synthesis of 1,8-Dioxodecahydroacridines Using Silica-Supported Polyphosphoric Acid (PPA-SiO₂) under Solvent-Free Conditions

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Abstract: Silica gel–supported polyphosphoric acid (PPA-SiO₂) was found to be an efficient catalyst for the synthesis of 1,8-dioxodecahydroacridines via one-pot three-component condensation of aryl aldehydes, dimedone, and ammonium acetate or 4-methyl aniline in high yields, easy workup procedure and short period of times. The catalyst was separated by simple filtration and used in the reaction three times without any significant loss of its activity.

Keywords: Decahydroacridine, One-pot reaction, Solvent-free, Silica-supported polyphosphoric acid (PPA-SiO₂).

Introduction

The principles of green chemistry have been introduced to eliminate or reduce the use of hazardous materials such as H₂SO₄ or H₃PO₄ in chemical processes. Cleaner technologies could be possible by making use of environmentally friendly materials involving the use of solid acids. These catalysts have many advantages over liquid acid catalysts¹⁻³. Recently, solid-supported reagents, such as silica gel-supported acids, have gained considerable interest in organic synthesis because of their unique properties of the reagents such as high efficiency due to more surface area, more stability and reusability, low toxicity, greater selectivity and ease of handling ^{4,5}. The 1,4-dihydropyridine (DHP) ring system is found in a variety of compounds including dyes, organic materials and pharmaceuticals. Among the pharmaceuticals, 1,4-dihydropyridines have been employed for the treatment of cardiovascular diseases, such as, angina pectoris⁶. 1,8-Dioxodecahydroacridines with a 1,4-dihydropyridine parent moiety, have received less attention than other 1,4-dihydropyridine derivatives. These compounds have been shown to have very high lasing efficiencies and used as

photoinitiators^{7,8}. Very few methods are known in the literature for the synthesis of acridinediones. The most straightforward synthesis of this compounds involve the threecomponent condensation of an aldehyde, dimedone, and ammonium acetate or appropriate amines in the presence of several catalysts such as *p*-dodecylbenezenesulfonic acid⁹, Amberlyst-15¹⁰, [Hmim]TFA¹¹, Tris(pentafluorophenyl)borane¹², FeCl₃-SiO₂¹³, Proline¹⁴, Acidic Ionic Liquids¹⁵, Brønsted acidic imidazolium salts¹⁶, Zn(OAC)₂.2H₂O¹⁷, Silica-Bonded *S*-Sulfonic Acid¹⁸ and Ceric ammonium nitrate (CAN)¹⁹. However, some of these methodologies encounter some limitations, such as long reaction times, unsatisfactory yields, harsh reaction conditions, expensive catalysts and tedious work-up procedure. Thus, As part of our current studies on the development of new routes for the synthesis of organic compounds using reusable catalysts ^{20,21}, in this context, we became interested to report a simple, efficient and eco-friendly synthesis of 1,8-dioxodecahydroacridines via three-component condensation of an aryl aldehyde, dimedone, and ammonium acetate or 4-methyl aniline using silica-supported polyphosphoric acid (PPA-SiO₂) as a reusable catalyst under solvent free conditions (Scheme 1).



Experimental

All chemicals were commercially available and used without further purification. All yields refer to isolated products after purification. Products were characterized by comparison of spectroscopic data (IR, ¹H NMR spectra) and melting points with authentic samples. The catalyst was synthesized according to the literature²². Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The ¹H NMR (500 MHz) spectra were recorded on Bruker DRX500 spectrometer in CDCl₃ relative to TMS.

General procedure for the synthesis of 1,8-dioxodecahydroacridines using PPA- SiO_2 as catalyst

A mixture of dimedone **1** (2 mmol), aromatic aldehyde **2a-h** (1 mmol), ammonium acetate (1 mmol) or 4-methyl aniline (1 mmol) and PPA-SiO₂ (0.02 g, 0.0100 mmol H^+)²² was heated on the oil bath at 100 °C for 5-25 min. The reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was cooled to room temperature and hot ethanol was added. The solid residue was dissolved in hot ethanol and filtered off. The crude product was collected from the filtrate after cooling to room temperature and recrystallized from ethanol to give compounds **3a-l** in high yields. All of the 1,8-dioxodecahydroacridine

derivatives are known and were identified by comparison of their physical and spectroscopic data (IR, NMR) with those of authentic samples^{8,16,17,23,24}.

Selected physical and ¹HNMR data of the products

3,3,6,6-Tetramethyl-9-(4-chlorophenyl)-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione (**3**) m.p. 299 – 301 °C ; ¹H NMR (CDCl₃, 500 MHz): δ 0.96 (s, 6H, 2CH₃), 1.09 (s, 6H, 2CH₃); 2.16 (d, J =16 Hz, 2H, H-2a,7b), 2.27 (d, J =16 Hz, 2H,H-2a',7b'), 2.28 (d, J =16.5 Hz, H-4c,5d), 2.35 (d, J =16.5 Hz, H-4c',5d'), 5.06 (s, 1H, H-9), 7.07 (brs, 1H, NH), 7.17 (d, J = 8.3 Hz, 2H, ArH), 7.29 (d, J = 8.3 Hz, 2H, ArH).

3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione (**8**) m.p 286-288 °C ¹H NMR (500 MHz, CDCl₃) δ: 0.85 (s, 6H, 2Me), 1.01 (s, 6H, 2Me), 1.96 (d, J=16.5 Hz, 2H, H-2a,7b),2.23 (d, J=16.5 Hz, 2H, H-2a',7b'), 2.33 (d, J=16.5 Hz,2H, H-4c,5d), 2.52 (d, J=16.5 Hz, 2H, H-4c',5d'), 4.90(s, 1H, H-9), 7.5 (d, J=8.5 Hz, 2H, ArH), 8.1 (d, J=8.5 Hz, 2H, ArH), 6.1 (brs, 1H, NH).

3,3,6,6-Tetramethyl-1,8-dioxo-9-(4-chlorophenyl)-10-(4-methylphenyl)-decahydro-acridine (**10**)

m.p. 270-271°C; ¹H NMR (500 MHz, CDCl₃): δ 0.80(s, 6H,), 0.94 (s, 6H), 1.83 (d, J = 17.4 Hz, 2H), 2.05–2.21 (m, 6H), 2.49(s, 3H), 5.23 (s, 1H), 7.08 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 7.6 Hz, 2H), 7.36 (t, J = 8.4 Hz, 4H).

Recycling of the catalyst

After the completion of the reaction, the reaction mixture was cooled to room temperature and hot ethanol was added. The catalyst was separated by simple filtration, dried at 100 °C under vacuum for 2 h and reused for the similar reaction. As it is shown in Figure 1, the catalyst could be reused at least three times without significant loss of activity.



Results and Discussion

To optimize the reaction conditions, the reaction of benzaldehyde (1 mmol), dimedone (2 mmol), and ammonium acetate (1 mmol) in the presence of PPA-SiO₂ (0.02 g) was selected as a model. The reaction was carried out in various solvents and under solvent-free conditions. As shown in Table 1, in comparison to conventional methods, the yields of the reaction under solvent-free conditions are greater and the reaction time is shorter. The shortest time and best yield were achieved at 100 °C. Next, to found the optimum quantity

of PPA-SiO₂, the reaction of benzaldehyde, dimedone and ammonium acetate was carried out under the previously mentioned conditions using different quantities of catalyst at 100 °C. The use of 0.02 g of catalyst resulted in the highest yield in 10 min.

Table 1. Synthesis of 1,8-dioxodecahydroacridine **3a** in the presence of PPA-SiO₂ (0.02 g, 0.0100 mmol H^+)²² in different solvents and optimization of temperature in solvent-free conditions.

Entry	Solvent	Temperature, °C	Time, min	Yield, % ^a
1	MeOH	64	300	Trace
2	EtOH	78	300	82
3	CH ₃ CN	81	300	85
4	H_2O	100	300	72
5	Solvent-free	70	110	62
7	Solvent-free	80	10	75
8	Solvent-free	100	10	92
9	Solvent-free	120	10	93

^aThe yields were calculated based on benzaldehyde and refer to the pure isolated product.

Thus, we prepared a range of 1,8-dioxodecahydroacridines under the optimized reaction conditions. In all cases, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the expected products in excellent yields and short reaction times. The kind of aldehyde has no significant effect on the reaction. The results are shown in Table 2. It was indicated that both electron rich and electron deficient aldehydes reacted well, mostly leading to high yields of products.

Entry	Ar	R'	Products ^b	Time min	Yield ^c	M.p., °C	
						Found	Reported
1	C_6H_5	Н	3a	10	93	192-195	$(190-192)^{23}$
2	$4-BrC_6H_4$	Н	3b	10	95	239-242	$(241-243)^{17}$
3	$4-ClC_6H_4$	Н	3c	5	92	300-302	$(299-301)^{17}$
4	$2-ClC_6H_4$	Н	3d	18	90	220-222	$(221-223)^8$
5	$4\text{-}OCH_3C_6H_4$	Н	3 e	14	89	270-272	$(270-272)^{24}$
6	$4-CH_3C_6H_4$	Н	3f	18	90	269-271	$(190-192)^8$
7	$3-NO_2C_6H_4$	Н	3g	13	88	288-291	$(288-290)^{17}$
8	$4-NO_2C_6H_4$	Н	3h	5	94	286-289	$(286-288)^{17}$
9	C_6H_5	$4-CH_3C_6H_4$	3i	25	87	260-263	$(260-262)^{16}$
10	$4-ClC_6H_4$	$4-CH_3C_6H_4$	3j	18	90	270-271	$(269-271)^{16}$
11	$4\text{-}OCH_3C_6H_4$	$4\text{-}CH_3C_6H_4$	3k	25	88	280-282	$(281-283)^{16}$
12	$3-NO_2C_6H_4$	$4-CH_3C_6H_4$	31	24	93	285-287	$(283-284)^{16}$

Table 2. Preparation of 1,8-dioxodecahydroacridines using PPA-SiO₂ (0.02 g, 0.010 mmol H^+)²² as catalyst^a.

^{*a*}The amount of PPA-SiO₂ as a catalyst was chosen (0.020 g, 0.010 mmol H^+) ²². ^{*b*} All products were characterized by use of ¹H NMR and IR spectral data, and comparison of their melting points with those of authentic samples. ^{*c*}Isolated yields.

The catalyst also showed excellent reusability in these reactions. The catalyst was recovered in excellent yields (91, 89 and 87% in Figure 1) and used in the reactions three times; it showed the same activity as fresh catalyst without any significant loss of its activity.

To show merit of the present work in comparison with reported results in the literature, we compared results of PPA-SiO₂ with tris(pentaflurophenyl)borane¹², Amberlyst-15¹⁰, proline¹⁴, ceric ammonium nitrate (CAN)¹⁹ and brønsted acidic imidazolium salts¹⁶ as catalysts in the reaction of benzaldehyde, dimedone and ammonium acetate. As shown in Table 3, PPA-SiO₂ can act as high efficiency catalyst with fast time and high yields of the obtained products.

Table 3. Comparison results of PPA-SiO₂ with tris(pentaflurophenyl)borane¹², Amberlyst-15¹⁰, proline¹⁴, ceric ammonium nitrate (CAN)¹⁹ and brønsted acidic imidazolium salts¹⁶ as catalysts in the reaction of benzaldehyde, dimedone, and ammonium acetate.

Entry	Catalyst	Time/min	Yield%
1	Tris(pentaflurophenyl)borane	168	80
2	Amberlyst-15	240	81
3	L - proline	300	98
4	Ceric ammonium nitrate (CAN)	240	98
5	Brønsted acidic imidazolium salts	240	85
6	PPA-SiO ₂	10	93

Conclusion

In conclusion, we have reported a new simple catalytic method for the synthesis of 1,8dioxodecahydroacridines by one-pot condensation reaction of aryl aldehydes, dimedone, and ammonium acetate or 4-methyl aniline using PPA-SiO₂ as an efficient, reusable and green heterogeneous catalyst under solvent-free conditions. The catalyst can be recycled after a simple work-up and reused at least three runs without appreciable reduction in its catalytic activity. High yields, short reaction times, easy work-up and absence of any volatile and hazardous organic solvents are some advantages of this approach.

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