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SILICA-SUPPORTED ANTIMONY(III) CHLORIDE AS HIGHLY EFFECTIVE AND REUSABLE HETEROGENEOUS CATALYST FOR THE SYNTHESIS OF 1,8-DIOXODECAHYDROACRIDINES

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Abstract: Antimony trichloride supported on silica ($SbCl_3$-SiO_2) has been found to be an efficientheterogeneous catalyst for the synthesis of 1,8-dioxodecahydroacridines by three-components condensation of dimedone, aromatic aldehydes and aromatic amines or ammonium acetate under solvent-free conditions. The present methodology offers several advantages such as high yields, short reaction times, simple operation and convenient work-up.Moreover, the catalyst could separated by simple filtration and used in the reaction three times without any significant loss of its activity.

Keywords: Antimony trichloride, 1,8-dioxodecahydroacridines,$SbCl_3/SiO_2$, solvent-free, heterogeneous catalyst.

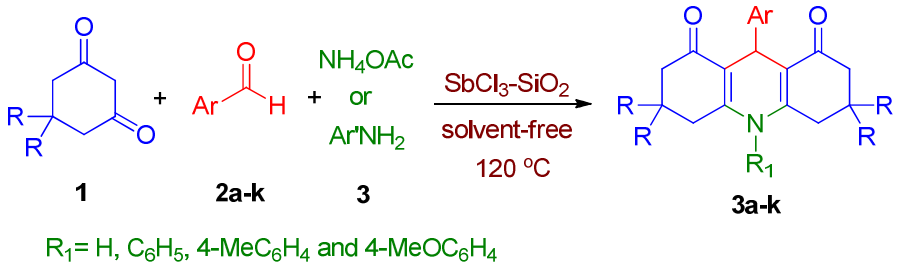
Introduction

Multicomponent reactions (MCRs) have emerged as efficient and powerful tools in modern synthetic organic chemistry because the synthesis of complex organic molecules from simple and readily available substrates can be achieved in a very fast and efficient manner without the isolation of any intermediate.[I-III] In this type of reactions three or more components are reacted to form ideally one product, which contains the essential parts of all the initial reactants. MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production. Therefore, developing new MCRs and improving known MCRs are popular areas of research in current organic chemistry.

1,4-Dihydropyridines (1,4-DHPs) are a common feature of various bioactive compounds such as vasodilator, bronchodilator, anti-atherosclerotic, anti-cancer and anti-diabetic agents.[IV-VII] Also, a number of DHP derivatives are employed as potential drug candidates for the treatment of congestive heart failure.[VIII] 1,8-Dioxodecahydroacridines and their derivatives are polyfunctionalized 1,4-dihydropyridine derivatives which have received less attention than other 1,4-dihydropyridine derivatives. These compounds are generally synthesized in a three component cyclocondensation of dimedone, aromatic aldehydes and ammonium acetate or amines in the presence of several catalysts such asBrønsted acidic

imidazoliumsalts,[IX]hydantoin,[X]saccharose,[XI]nanomagnetic supported ferric hydrogen sulfate,[XII]ammonium chloride,[XIII]boron trifluoride,[XIV]Fe-ZrO_2,[XV] nanocrystalline TiO_2,[XVI]*p*-dodecylbenzenesulfonic acid (DBSA),[XVII]carbon based solid acid,[XVIII] $[B(C_6F_5)_3]$,[XIX]Proline,[XX]andAmberlyst-15.[XXI]Synthesis of these compounds by the classical Hantzsch'sprocedure[XXII] or reaction of aldoximes with dimedone, under microwave irradiation have also been reported.[XXIII] However, most of these reported procedures have disadvantages including low yields, prolonged reaction time, toxic organic solvents and harsh reaction conditions. Therefore, the development of simple, efficient, high-yielding, and environmentally friendlymethods under mild conditions using new catalysts for the synthesis of 1,8-dioxodecahydroacridines is still necessary.

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 caused by more surface area, more stability and reusability, low toxicity, greater selectivity and ease of handling.[XXIV] In recent years, silica supported antimony trichloride has been used as catalyst in many important organic reactions,[XXV-XXVII] because this compound not only is commercially available and inexpensive, but also is easier to handle than other metal halides such as $InCl_3$, $GdCl_3$, and $TiCl_4$.[XXVIII] In continuation of our work on new synthetic methodologies,[XXIX-XXXIX] we wish to report an efficient method for the synthesis of 1,8-dioxodecahydroacridines in high yields in the presence $SbCl_3$-SiO_2 as heterogeneous and reusable catalyst under solvent free conditions (Scheme 1).



Scheme 1. Synthesis of 1,8-dioxodecahydroacridines in the presence of $SbCl_3$-SiO_2

Results and Discussion

One-pot synthesis of 1,8-dioxodecahydroacridines

In order to optimize the reaction conditions, the reaction of dimedone**1** (2 mmol) 4-bromobenzaldehyde **2a**(1 mmol)and ammonium acetate **3**(1 mmol) in the presence of $SbCl_3$-SiO_2 as a catalystwas studied (Table 1) in different polar solvents (Entries 2-4) and under solvent-free conditions at different temperatures (Entries 5-8). Also, the effect of the catalyst loading on the model reaction was studied (Entries 9,10). The best result was obtained at 120 ºC for 30 min using 0.02 g of the catalyst under solvent-free conditions (Entry 7).

Table 1. Screening of the reaction conditions for the synthesis of **4b**[a]

Entry	Catalyst (gr)	Conditions	Time (min)	Temperature (°C)	Yield (%)[b]
1	None	Solvent-free	120	120	---
2	0.02	EtOH	60	ref	63
3	0.02	MeOH	60	ref	60
4	0.02	H_2O	60	ref	55
5	0.02	Solvent-free	30	80	67
6	0.02	Solvent-free	30	100	80
7	0.02	Solvent-free	30	120	90

8	0.02	Solvent-free	30	130	90
9	0.01	Solvent-free	30	120	72
10	0.03	Solvent-free	30	120	91

[a] Reaction conditions: dimedone (2 mmol), 4-bromobenzaldehyde (1 mmol), and ammonium acetate (1 mmol).
[b] Isolated yields

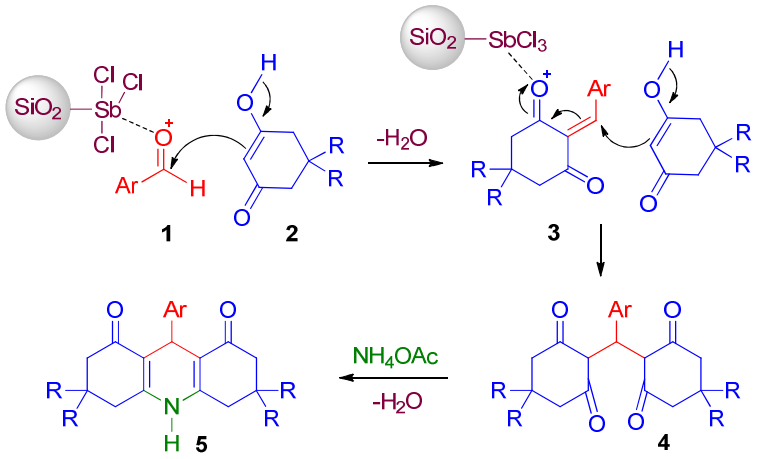
To assess the efficiency of $SbCl_3$-SiO_2 in the preparation of 1,8-dioxodecahydroacridines, dimedone **1** were reacted with various aromatic aldehydes **2a-k** and ammonium acetate or armatic amines **3** under optimal reaction conditions (Table 1, Entry 7). These results show that the requested reactions efficiently occurred with excellent yields in very short times (Table 2). It seems that the electronic nature of the functional group on the ring of the aldehyde exerted a slight influence on the reaction time and yield.

Table 2. Preparation of 1,8-dioxodecahydroacridines using $SbCl_3$-SiO_2 as catalyst[a]

Entry	Ar	R	R_1	Product[b]	Time (min)	Yields (%)[c]	Mp ºC	
							Found	Reported
1	C_6H_5	CH_3	H	**4a**	45	86	190-192	190-192[XXII]
2	4-BrC_6H_4	CH_3	H	**4b**	30	90	242-244	241-243[XIII]
3	4-ClC_6H_4	CH_3	H	**4c**	25	90	298-300	294-296[XIII]
4	4-$NO_2C_6H_5$	CH_3	H	**4d**	60	88	285-287	286-289[XVIII]
5	C_6H_5	H	H	**4e**	15	87	280-282	279-281[X]
6	4-ClC_6H_4	H	H	**4f**	30	92	265-267	268-270[X]
7	4-ClC_6H_5	CH_3	4-MeC_6H_4	**4g**	30	88	270-272	270-271[XVIII]
8	C_6H_5	CH_3	4-$MeOC_6H_4$	**4h**	25	86	210-212	215-217[XIII]
9	4-MeC_6H_4	CH_3	4-MeC_6H_4	**4i**	30	73	291-293	293-294[XXI]
10	4-$MeOC_6H_4$	CH_3	4-MeC_6H_4	**4j**	40	79	281-282	281-283[IX]
11	C_6H_5	CH_3	C_6H_5	**4k**	30	90	253-255	254-256[XXI]

[a] Reaction conditions: dimedone**1**(2 mmol), aromatic aldehyde **2a-k**(1 mmol), and ammonium acetate or aromatic amine**3** (1 mmol) in presence of 0.02 g of catalystat 120 ºC under solvent-free conditions.
[b]All the products were characterized by comparison of their melting points with those of authentic samples. Also the structures of some products were confirmed by ^{1}H NMR and IR spectral data.
[c] Isolated yields.

According to proposed mechanism in the literature,[XII]at the firststep, from the initial condensation of aromatic aldehyde **1** and dimedone**2** that their carbonyl groups are activated with catalyst, the intermediate **3** is formed (Scheme 2). Then, another dimedone reacts with activated intermediate **3** and intermediate **4** is created. Finally, from the nucleophilic attack of ammonium acetate to intermediate **4**, and then elimination of two mole of water, desired 1,8-dioxodecahydroacridine **5**isproduced.



Scheme 2. Proposed mechanism for the synthesis of 1,8-dioxodecahydroacridines catalyzed by $SbCl_3$-SiO_2

In order to examine the recyclability of $SbCl_3$-SiO_2, the model reaction was again carried out.After completion the reaction, the catalyst was recovered by filtration,washedwith acetone and dried at 100 ^oC for 2h. The recovered catalyst was re-used three timesin the model reaction, to afford 90%, 89%,and 87% yields, respectively.

Conclusion

$SbCl_3$-$SiO_2$was successfully used as a Lewis acid heterogeneous catalyst for thesynthesis of 1,8-dioxodecahydroacridinesat 120 °C under solvent-free conditions. Thecatalyst was recovered after a very simple work-up and reused at least three times without appreciable loss of catalytic activity. The present method requires a small amount (0.02 g) of a non-toxic and inexpensivematerial ($SbCl_3$-SiO_2) as the catalyst. Good to high yields, short reaction times, easy work-upand absence of any volatile and hazardous organic solvents are some of the advantages of this protocol.

Experimental

General

All chemicals were purchased from Merck, Aldrich and Fluka Chemical Companies and used without further purification.Melting points were recorded on a Stuart SMP3 melting point apparatus. The IR spectra were obtained using a 4300 Shimadzu spectrophotometer as KBr disks. The ^1H NMR (400 and 500 MHz) spectra were recorded with Bruker DRX400 and 500 spectrometers.

Preparation of $SbCl_3$-SiO_2

Antimony trichloride (2.28 g, 10 mmol) was added to a suspension of silica (250–400 mesh, 27.8 g) in ethanol (50.0 mL). The mixture was stirred at room temperature for 1 h. The solvent was removed with a rotary evaporator and the residue was heated at 100 ^oC under vacuum for 5 h to furnish $SbCl_3$-SiO_2 as a white free-flowing powder.[25]

General procedure for synthesis of 1,8-dioxodecahydroacridines 4a-k

A mixture of dimedone**1** (2 mmol), aromatic aldehydes**1a-k** (1 mmol),ammonium acetate or aromatic amines**3**(1 mmol) and $SbCl_3$-SiO_2 (0.02 g) was heated in the oil bath at 120 °C for 15-60min. During the procedure, the reaction was monitored by TLC. Upon completion, hot ethanol was added to reaction mixture. The catalyst was insoluble in ethanol and could be separated from the product by filtration.The product was collected after evaporated the solvent and then recrystallized from ethanol to give compounds **4a-k**in high yields.

Selected ^{1}H NMR and FT-IR Data

3,3,6,6-Tetramethyl-1,8-dioxo-9-(4-nitrophenyl)-decahydroacridine (**4d**): (500 MHz, $CDCl_3$) δ 1.00 (s, 6H, 2Me), 1.14 (s, 6H, 2Me), 2.19 (d, J = 16.5 Hz, 2H), 2.28 (d, J = 16.5 Hz, 2H), 2.32 (d, J = 16.8 Hz, 2H), 2.46 (d, J = 16.8 Hz, 2H), 5.19 (s, 1H, CH), 6.12 (s br., 1H, NH), 7.54 (d, J = 8.8 Hz, 2H, arom-H), 8.10 (d, J = 8.8 Hz, 2H, arom-H); IR (KBr disc): υ 3432, 3279, 3056, 2957, 1650, 1610, 1489, 1366, 1222 cm^{-1}.

3,3,6,6-Tetramethyl-1,8-dioxo-9-(4-chlorophenyl)-10-(4-methylphenyl)-decahydroacridine (**4g**): (500 MHz, $CDCl_3$) δ 0.83 (s, 6H, 2Me), 0.97 (s, 6H, 2Me), 1.86 (d, J =17.5 Hz, 2H), 2.09 (d, J = 17.5 Hz, 2H), 2.15 (d, J = 16.5 Hz, 2H), 2.22 (d, J = 16.5 Hz, 2H), 2.52 (s, 3H, Me), 5.27 (s, 1H, CH), 7.11 (d, J = 8.2 Hz, 2H, arom-H), 7.24 (d, J = 8.3 Hz, 2H, arom-H), 7.37 (d, J = 8.7 Hz, 2H, arom-H), 7.39 (d, J = 8.7 Hz, 2H, arom-H); IR (KBr disc): υ3175, 3059, 2957, 1649, 1609, 1489, 1362, 1220 cm^{-1}.

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