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$SbCl_3$-SiO_2AS AN EFFICIENT AND HETEROGENEOUS CATALYST FOR THE SYNTHESIS OF POLYHYDROQUINOLINE DERIVATIVES UNDER SOLVENT-FREE CONDITIONS

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Abstract:A simple and efficient one pot approach toward the synthesis of polyhyroquinoline and 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines through the four-component reaction of dimedone or 1,3-cyclohexanedione, aromatic aldehydes, ammonium acetate, and ethylacetoacetate or meldrum acid in presence ofantimony trichloride supported on silica ($SbCl_3$-SiO_2) at 120 ^oC under solvent-free conditions has been developed in good to excellent yields**.** The heterogeneous Lewis acid catalyst could be recovered easily and reused many times without significant loss of its catalytic activity.

Keywords: Polyhyroquinoline, 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines, antimony trichloride, supported heterogeneous catalyst, solvent-free.

Introduction

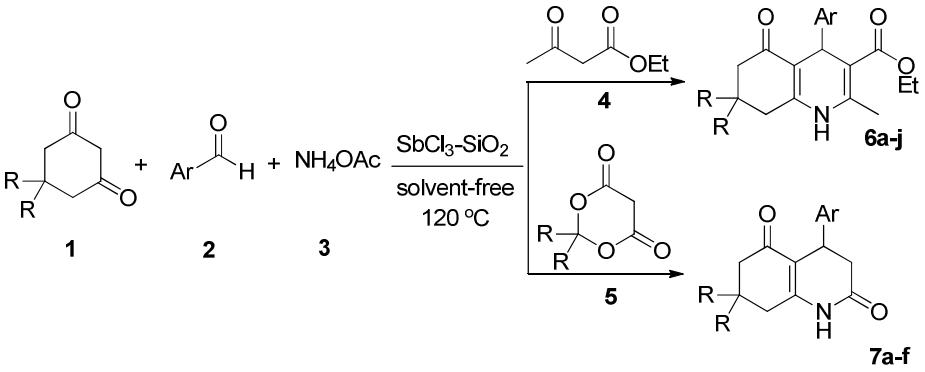
The principles of green chemistry have been introduced to eliminate or at least to reduce the use of hazardous materials, such as H_2SO_4 or H_3PO_4 in chemical processes. Cleaner technologies could become possible by making use of the environmental friendly materials, such as the use of solid supported acids. These catalysts have many advantages over liquid acid catalysts.[I-III]They are not corrosive but environmentally benign, presenting fewer disposal problems. Thus the development and use of solid green catalysts isvery important in organic syntheses.

The use of reagents supported on inorganic supports [IV-VI]have gained considerable interests in organic synthesis because of their unique properties, such as simple work-up and product purification, high stability and reusability, low toxicity, enhanced or reduced reactivity of the functional groups, selectivity that may be different from that in solution, and manipulative simplicity.[VII-IX]Although the catalytic applications of silica supported reagents for organic synthesis have been established, to the best of our knowledge, there is no published report on the use of $SbCl_3$-SiO_2 in the synthesis of polyhyroquinoline and 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines.

Polyhydroquinoline and 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines derivatives are very well-known molecules that include a six-membered heterocyclic ring, which have been reported to possess a wide range of biological properties and pharmaceutical activitiessuch as

vasodilator, antitumor, bronchodilator, antiartherosclerotic, geroprotective and hepatoprotectiveactivity.[X-XV] Thus, the synthesis of these heterocycles has become an area of great interest.

Due to their importance, many classical methods have been reported for synthesis of this category of compounds in presence of various conditions and catalysts such as Co_3O_4-CNTs,[XVI] Fe_3O_4@chitosan,[XVII] SBA-15/SO_3H,[XVIII] molecular iodine,[XIX] ceric ammonium nitrate,[XX] Hafnium(IV)bis(perfluorooctanesulfonyl)imide,[XXI] carbon based solid acid,[XXII] PPA-SiO_2,[XXIII] guanidine hydrochloride,[XXIV] trifluoroethanol,[XXV] Pd-nanoparticles,[XXVI] and silica-based sulfonic acid.[XXVII] Although all of the above synthetic methods have advantages, they also have some limitations such as low yields, high temperatures, difficult preparation of catalysts and long reaction time. In order to overcome the mentioned limits and disadvantages of the above methods and also, in continuation of our work on new synthetic methodologies,[XXVIII-XL] we wish to report an efficient method for the synthesis of polyhydroquinoline and 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines derivatives in high yields in the presence antimony trichloride supported on silica as heterogeneous Lewis acid catalyst under solvent free conditions (Scheme 1).



Scheme 1. Synthesis of polyhydroquinoline**6a-j** and 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines **7a-f**derivatives in the presence of $SbCl_3$-SiO_2as a reusable catalyst.

Results and Discussion

At first, in order to explore the catalytic activity of catalyst ($SbCl_3$-SiO_2), the four-component reaction of dimedone, benzaldehyde, ammonium acetate and ethyl acetoacetate was carried out as a model reaction. Temperature, solvent-free conditions as well as the use of various solvents such as dichloromethane, ethanol, methanol and water (Table 1) were investigated; no product was obtained in the absence of the catalyst (Entry 1). The yields of the reaction were better in solvent-free conditions than in presence of solvents (Entries 2-5).Increasing the temperature improve the yields of the reaction (Entries 6-10). The best result was at 120 ^oC under solvent-free conditions (Entry 9). Moreover, when the model reaction was carried out in presence of $SbCl_3$ and SiO_2in the same time and conditions,yield of the reaction was lower than when $SbCl_3$-SiO_2 was used as a catalyst (Entries 11 and 12).

Table 1. Comparison of different conditions and temperatures for the synthesis of**6b**[a]

Entry	Catalyst	Conditions	Time (min)	Temperature (°C)	Yield (%)[b]
1	Without catalyst	Solvent-free	60	120	---
2	$SbCl_3$-SiO_2	CH_2Cl_2	30	reflux	low
3	$SbCl_3$-SiO_2	EtOH	30	reflux	55
4	$SbCl_3$-SiO_2	MeOH	30	reflux	44
5	$SbCl_3$-SiO_2	H_2O	30	reflux	62

6	$SbCl_3$-SiO_2	Solvent-free	30	rt	35
7	$SbCl_3$-SiO_2	Solvent-free	15	80	75
8	$SbCl_3$-SiO_2	Solvent-free	15	100	83
9	$SbCl_3$-SiO_2	Solvent-free	15	120	92
10	$SbCl_3$-SiO_2	Solvent-free	15	130	92
11	$SbCl_3$	Solvent-free	30	120	85
12	SiO_2	Solvent-free	30	120	---

[a] Reaction conditions: dimedone (1mmol), benzaldehyde (1 mmol), ammonium acetate (3mmol) and ethyl acetoacetate (1.2mmol) in presence of $SbCl_3$-SiO_2.
[b] Isolated yields.

Next, the model reaction was carried out under the previously mentioned conditions using different amounts of catalyst to find the optimum quantity of $SbCl_3$-SiO_2 (Table 2). As mentioned before, no product was obtained in the absence of the catalyst (Entry 1). Increasing the amount of the catalyst improved the yield of **6b** (Entries 2–4), with the use of 0.025 g of catalyst resulted in the highest yield in 15 min (Entry 4). Further increase of the amount of the catalyst failed to affect the yield noticeably (Entries 5 and 6).

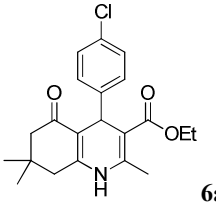
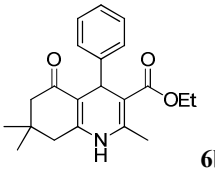
Table 2. Comparison of the amount of $SbCl_3$-SiO_2 for the synthesis of**6b**[a]

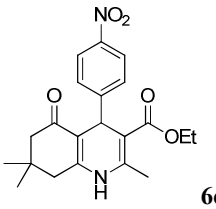
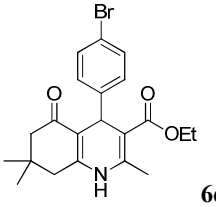
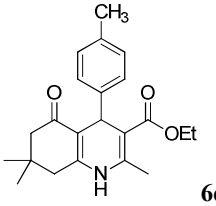
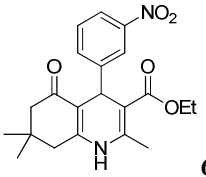
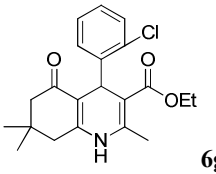
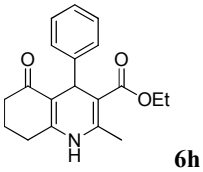
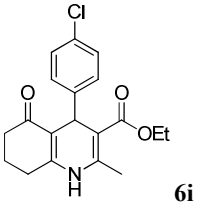
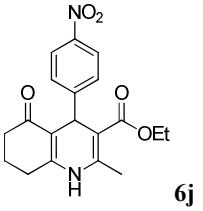
Entry	Catalyst amount (g)	Conditions	Time (min)	Yield (%)[b]
1	None	Solvent-free/120 ^oC	60	---
2	0.005	Solvent-free/120 ^oC	15	32
3	0.010	Solvent-free/120 ^oC	15	61
4	0.025	Solvent-free/120 ^oC	15	95
5	0.035	Solvent-free/120 ^oC	15	92
6	0.050	Solvent-free/120 ^oC	15	93

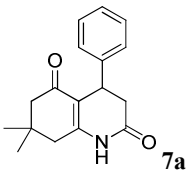
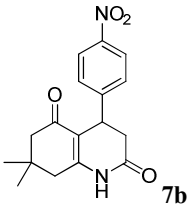
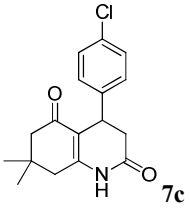
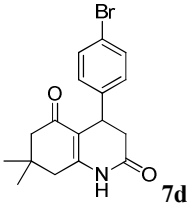
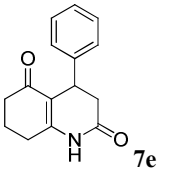
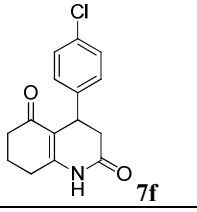
[a] Reaction conditions: dimedone (1 mmol), benzaldehyde (1 mmol), ammonium acetate (3mmol) and ethyl acetoacetate (1.2mmol) in presence of $SbCl_3$-SiO_2 at 120 ^oC under solvent-free conditions.
[b] Isolated yields.

The optimized conditions having been determined, the scope and efficiency of the reaction were investigated for the preparation of a variety of substituted polyhyroquinoline **6a-j**and 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines**7a-f**in the presence of $SbCl_3$-SiO_2 using a number of aromatic aldehydes bearing both electron-donating and electron-withdrawing substitutents. Good to excellent yields were obtained as illustrated in Table 3.

Table 3. Synthesisof polyhyroquinoline **6a-j**[a] and 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines**7a-f**[b]using $SbCl_3$-SiO_2 as catalyst.

Entry	Ar	R	Product	Time (min)	Yields (%)[c]
1	4-ClC_6H_4	CH_3	 **6a**	30	88
2	C_6H_5	CH_3	 **6b**	15	92

3	4-$NO_2C_6H_5$	CH_3	 **6c**	40	83
4	4-BrC_6H_5	CH_3	 **6d**	25	87
5	4-$CH_3C_6H_4$	CH_3	 **6e**	15	92
6	3-$NO_2C_6H_5$	CH_3	 **6f**	35	88
7	2-ClC_6H_4	CH_3	 **6g**	40	80
8	C_6H_5	H	 **6h**	20	91
9	4-ClC_6H_4	H	 **6i**	15	86
10	4-$NO_2C_6H_4$	H	 **6j**	20	90

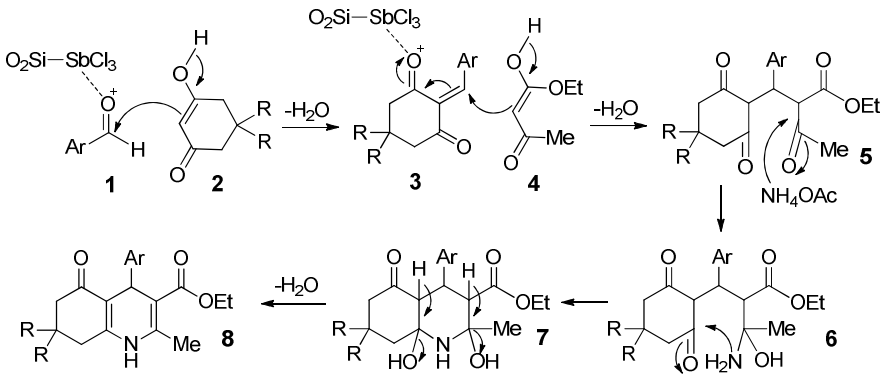
11	C_6H_5	CH_3	 **7a**	45	82
12	4-$NO_2C_6H_4$	CH_3	 **7b**	15	84
13	4-ClC_6H_4	CH_3	 **7c**	25	90
14	4-BrC_6H_4	CH_3	 **7d**	30	91
15	C_6H_5	H	 **7e**	15	86
16	4-ClC_6H_4	H	 **7f**	30	92

[a] Reaction conditions: dimedone or 1,3-cyclohexanedione**1**(1mmol), aromatic aldehyde **2**(1 mmol), ammonium acetate**3** (3mmol) and ethyl acetoacetate **4** (1.2mmol) in presence of 0.025 g of catalyst at 120 ºC under solvent-free conditions.

[b] Reaction conditions: dimedone or 1,3-cyclohexanedione**1** (1 mmol), aromatic aldehyde **2** (1 mmol), ammonium acetate **3** (3mmol) and meldrum acid **5** (1 mmol) in presence of 0.025 g of catalyst at 120 ºC under solvent-free conditions.

[c] Isolated yields.

Based on the proposed mechanism in the literature,[XVI] it is reasonable to assume that polyhyroquinoline derivativesare formed from the initial condensation of aromatic aldehyde **1** and dimedone**2** that their carbonyl groups are activated with $SbCl_3$-SiO_2 to give intermediate**3** (Scheme 2). Next, the activated intermediate **3**could react with ethyl acetoacetate**4** to produce intermediate**5**. Then, from the nucleophilic attack of ammonium actetateto intermediate **5**, intermediate **6** is created. Finally, desired polyhyroquinoline derivatives **8**are formedby the elimination of two mol of water from the intermediate **7**.



Scheme 2.Proposed mechanism for synthesis of polyhyroquinoline derivatives 8.

The recyclability of the catalyst in the reaction of dimedone, benzaldehyde, ammonium acetate and ethyl acetoacetate (model reaction) in presence of $SbCl_3$-SiO_2(0.025 g) was also studied.After completion the reaction, the catalyst was recovered by filtration,washedwith acetone and dried at 100 ^oC for 2 h. As is shown in Fig. 1, the catalyst could be reused at least five times without significant loss of activity.

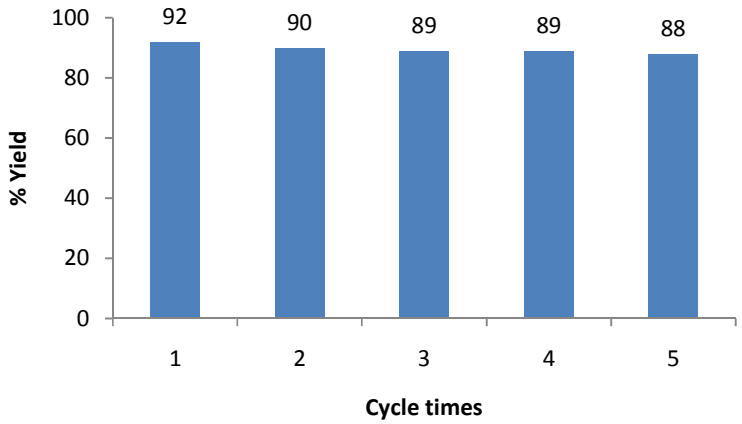


Fig. 1 Recycling experiment for $SbCl_3$–SiO_2

Conclusion

In conclusion, we report a simple and green catalytic method for the synthesis of polyhyroquinoline and 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines by one-pot condensation reaction of dimedone, aromatic aldehydes, ammonium acetate and ethyl acetoacetate or meldrum acid using $SbCl_3$–SiO_2 (0.025 g) as an efficient, reusable and green heterogeneous catalyst under solvent-free conditions. High yields, short reaction times, easy work-up, and absence of any volatile and hazardous organic solvents are some advantages of this protocol.

Experimental

General

All chemicals were purchased from Merck, Aldrich and Fluka Chemical Companies and used without further purification.

Preparation of catalyst

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 ^{o}C under vacuum for 5 h to furnish $SbCl_3$-SiO_2 as a white free-flowing powder(29.0g, 96 % yield).[XLI]

General procedure for synthesis of Polyhydroquinolines derivatives 6a-j

A mixture of dimedone or 1,3-cyclohexanedione **1**(1 mmol), aromatic aldehyde **2**(1 mmol), ammonium acetate **3** (3 mmol), ethylacetoacetate**4** (1.2 mmol) and $SbCl_3$-SiO_2(0.025 g) was heated on an oil bath at 120°C for appropriate times (see Table 3). Completion of the reaction was indicated by TLC (hexane:ethyl acetate, 2:1). After completion, appropriate amount of hot EtOH (96%) was added and the mixture stirred for 2 min. The heterogeneous catalyst was separated from the reaction mixture by filtration. The resulting crude product was poured into crushed ice, and the solid product which separated was isolated by filtration and recrystallized from ethanol (5 ml) to afford polyhydroquinolines**6a-j**.

General procedure for synthesis of 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines 7a-f

A mixture of dimedone or 1,3-cyclohexanedione **1** (1 mmol), aromatic aldehyde **2** (1 mmol), ammonium acetate **3** (3 mmol), meldrum acid **5** (1 mmol) and $SbCl_3$-SiO_2(0.025 g) was heated on an oil bath at 120°C for appropriate times (see Table 3). Completion of the reaction was indicated by TLC (hexane:ethyl acetate, 2:1). After completion, appropriate amount of hot EtOH (96%) was added and the mixture stirred for 2 min. The heterogeneous catalyst was separated from the reaction mixture by filtration. The resulting crude product was poured into crushed ice, and the solid product which separated was isolated by filtration and recrystallized from ethanol (5 ml) to afford polyhydroquinolines **7a-f**.

Analytical data

2,7,7-Trimethyl-5-oxo-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (entry 1): ^{1}H NMR (500 MHz, $CDCl_3$): δ0.94 (s, 3H), 1.08 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H), 2.12–2.34 (m, 4H), 2.37 (s, 3H), 4.06 (q, J = 7.1 Hz, 2H), 5.04 (s, 1H), 6.46 (brs, 1H, NH), 7.15–7.19 (d, J = 8 Hz, 2H), 7.24–7.26 (d, J = 8 Hz, 2H).

2,7,7-Trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (entry 2): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (s, 3H), 1.06 (s, 3H), 1.20 (t, 3H, J = 7.1 Hz), 2.12–2.28 (m, 4H), 2.34 (s, 3H), 4.05 (q, 2H, J = 7.1 Hz),5.06 (s, 1H), 6.63 (brs, 1H, NH), 7.07–7.12 (m, 1H), 7.17–7.22 (m, 2H), 7.27–7.32 (m, 2H).

2,7,7-Trimethyl-5-oxo-4-(3-nitrophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (entry 6): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (s, 3H), 1.09 (s, 3H), 1.2 (t, 3H, J = 7.3 Hz), 2.2–2.4 (m, 4H), 2.5 (s, 3H), 4.00 (q, 2H, J = 7.3 Hz), 5.05 (s, 1H), 6.01 (brs, 1H, NH), 7.5 (d, 2H, J = 9.2 Hz), 8.1 (d, 2H, J = 9.2 Hz).

Acknowledgments

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