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Silica Sulfuric Acid: An Efficient and Versatile Catalyst for One-Pot Synthesis of Substituted 5-Oxo-1,4,5,6,7,8-hexahydroquinoline Derivatives

XIN-YING QIN, TONG-SHOU JIN*, ZUN-XIA ZHOU and TONG-SHUANG LI
College of Chemistry and Environmental Science, Hebei University, Baoding 071002, P. R. China
E-mail: jintongshou@yahoo.com.cn

An easy method for synthesis of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives from 5,5-dimethyl-1,3-cyclohexanedione or 1,3-cyclohexanedione, arylaldehyde, methyl acetoacetate and ammonium acetate using silica sulfuric acid as catalyst is described. This method provides several advantages such as simple work-up procedure, mild conditions, high yields and environmental friendly, which makes it useful and attractive process for the synthesis of these compounds.

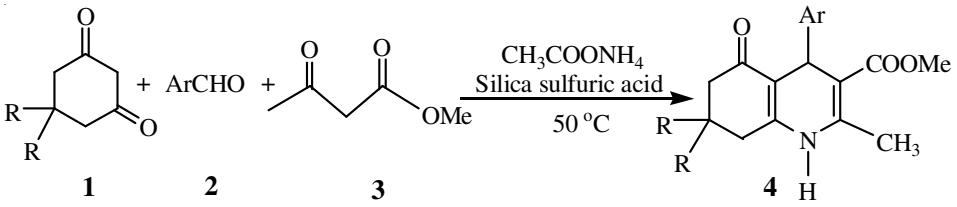
Key Words: Substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives, Cyclohexanedione, Arylaldehydes, Methyl acetoacetate, Silica sulfuric acid.

INTRODUCTION

It is known that quinolines and their derivatives are very useful compounds because a large number of natural products and drugs contain this heterocyclic unit[1-3]. They have attracted strong interest due to their useful biological and pharmacological properties, such as antitumor, antiviral, antitubercle, antidiabetic and antibacterial activities[4-8]. The remarkable drug activity of these compounds not only attracted many chemists to synthesize this heterocyclic nucleus but also became an active research area of continuing interest.

Substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives is a type of 1,4-dihydropyridine compounds[9]. Usually these compounds are synthesized from aldehydes, cyclohexanedione, ethyl acetoacetate and ammonium acetate or ammonium hydroxide in organic solvents[10-14]. Some of the methods were developed for the synthesis of 1,4-dihydropyridines, which comprise at high temperature in refluxing solvent[15,16], the use of microwave[17,18], ionic liquid[19,20], TMSCl-NaI[21] and metal triflates[22]. Each of the above methods has its own merit. However, some methods have not been entirely satisfactory, owing to such drawbacks as the use of high temperatures, expensive metal precursors, excess of organic solvent, long reaction time, low product yields and harsh refluxing conditions and requiring of a microwave equipment. Thus, the development of a simple, efficient and versatile method for the preparation of 1,4-dihydropyridine derivatives is an active area of research and there is a scope for further improvement towards milder reaction conditions and higher product yield.

Silica sulfuric acid is a kind of new type of solid acid, which has been extensively used in organic synthesis[23-27] due to its strong acidity, cheap, non-corrosive nature, reusability and non-polluting nature. Therefore, we are interested in using this inorganic acidic salts as a new sulfuric acid function. Herein we describe an easy and efficient method for synthesis of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives from 5,5-dimethyl-1,3-cyclohexanedione or 1,3-cyclohexanedione, arylaldehyde, methyl acetoacetate and ammonium acetate using silica sulfuric acid as catalyst under mild conditions (**Scheme-I**).



1 **2** **3** **4**

A: R=R=H, B: R=R=Me

Scheme-I

EXPERIMENTAL

Silica sulfuric acid was prepared by known methods[23,24]. Liquid aldehydes were distilled before use. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). ^{1}H NMR spectra were measured on a Bruker Avance 400 (400 MHz) spectrometer using TMS as internal reference and DMSO-d_6 as solvent. Elemental analyses were determined using Perkin-Elmer 2400 II elemental analyzer.

Procedure for the preparation of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives: A mixture of 5,5-dimethyl-1,3-cyclohexadione or 1,3-cyclohexadione **1** (1.0 mmol), aromatic aldehyde **2** (1.0 mmol), methyl acetoacetate **3** (1.5 mmol), ammonium acetate (2.0 mmol) and silica sulfuric acid (100 mg) was added into the reaction flask, followed by few drops (8-10 drops) of ethanol. The mixture was stirred at 50 °C for 3.0-5.5 h. The progress of the reaction was monitored by thin layer chromatograph. After completion of the reactions, ethyl acetate (40 mL) was added into the mixture and the catalyst silica sulfuric acid was filtered off and recycled. The filtrate was washed with saturated $NaHSO_3$ solution (20 mL) and brine (2 × 15 mL) successively. After drying ($MgSO_4$), the solvent was evaporated under reduced pressure and the crude product was obtained. The crude products were purified by recrystallization from ethanol (95 %) to give the pure products **4**.

RESULTS AND DISCUSSION

In a typical general experimental procedure, a mixture of 5,5-dimethyl-1,3-cyclohexanedione or 1,3-cyclohexanedione **1**, arylaldehyde **2**, methyl acetoacetate **3** and ammonium acetate was stirred at 50 °C in a few drops of ethanol with silica sulfuric acid as catalyst, the corresponding substituted 5-oxo-1,4,5,6,7,8-hexa-

hydroquinoline derivatives **4** were obtained in good to excellent yields. The results are summarized in Table-1.

TABLE-1
SYNTHESIS OF SUBSTITUTED 5-OXO-1,4,5,6,7,8-HEXAHYDROQUINOLINE DERIVATIVES CATALYZED BY SILICA SULFURIC ACID

Entry	Ar	R	Time (h)	Product	Yield* (%)	m.p. (ºC)	
						Found**	Reported[28]
1	2-$NO_2C_6H_4$ (**1a**)	CH_3	4.0	**4a**	92	273-275	274-276
2	3-$NO_2C_6H_4$ (**1b**)	CH_3	3.0	**4b**	94	223-224	222-223
3	4-$NO_2C_6H_4$ (**1c**)	CH_3	3.0	**4c**	95	252-254	251-253
4	2,4-$Cl_2C_6H_3$ (**1d**)	CH_3	4.0	**4d**	94	250-252	250-252
5	4-BrC_6H_4 (**1e**)	CH_3	4.5	**4e**	92	262-264	263-264
6	4-$CH_3C_6H_4$ (**1f**)	CH_3	5.0	**4f**	90	250-252	251-253
7	4-$CH_3OC_6H_4$ (**1g**)	CH_3	5.5	**4g**	88	255-256	256-257
8	3-$NO_2C_6H_4$ (**1h**)	H	3.0	**4h**	93	204-206	205-207
9	3-ClC_6H_4 (**1i**)	H	4.5	**4i**	87	256-258	257-259
10	4-BrC_6H_4 (**1j**)	H	3.5	**4j**	86	226-228	227-228
11	4-$CH_3C_6H_4$ (**1k**)	H	5.0	**4k**	85	238-240	239-241
12	4-$CH_3OC_6H_4$ (**1l**)	H	5.5	**4l**	83	221-223	222-224
13	3,4-$OCH_2OC_6H_3$ (**1m**)	H	5.0	**4m**	85	258-260	259-261

*Isolated yield; **After recrystallization.

As shown in Table-1, we can find the effect of electron and the nature of substituents on the aromatic ring did not show strongly obvious effects in terms of yields under this reaction conditions. Aromatic aldehydes containing electron-withdrawing groups (such as nitro group, halide) or electron-donating groups (such as alkyl group, alkoxyl group) were employed and reacted well to give the corresponding substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives in good to excellent yields.

The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields. Taking the 4-nitrobenzaldehyde was reacted with 5,5-dimethyl-1,3-cyclohexanedione **1**, **3** and ammonium acetate as an example, the reaction can not carried out in the absence of the catalyst when the mixture was heated at 50 °C for 3 h.

We have also studied the effect of the amount of the catalyst on this reaction. When the mixture was heated (**entry 3**) in the presence of silica sulfuric acid (60 mg), it gave the product **4c** in the yield of 78 % at 50 °C for 3 h. Increasing of the catalyst to 80, 90, 100 and 110 mg, it could obtain the yields to 86, 92, 95 and 95 %, respectively. Higher amounts of the catalyst did not improve the results to a greater extent. Thus, 100 mg silica sulfuric acid was chosen as a quantitative catalyst for these reactions.

The catalyst were easily regenerated by washing with ethyl acetate, followed by drying at 80 °C for 2 h. The catalyst could be reused 5 times for the synthesis of **4c** without significant loss of activity.

In conclusion, we have described a general and highly efficient procedure for the preparation of substituted 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives using the silica sulfuric acid as catalyst. This procedure offers several advantages including mild reaction conditions, cleaner reaction, high yields of products as well as a simple experimental and isolated procedure which makes it useful and attractive process for the synthesis of these compounds.

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