$Al_2(SO_4)_3$ IS AN EFFICIENT AND MILD ACID CATALYST FOR THE ONE-POT, FOUR-COMPONENT SYNTHESIS OF POLYHYDROQUINOLINE

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ABSTRACT

Aluminium sulfate has mild acidity, yet the acidity of aluminium sulfate is not taken advantage of in organic synthesis. Here, we utilized aluminium sulfate for the first time in a multicomponent reaction for the synthesis of polyhydroquinoline. A four-component one-pot synthesis of polyhydroquinoline was carried out by condensing dimedone, aromatic aldehyde, ethyl acetoacetate, and ammonium acetate using a catalytic amount of aluminium sulfate (10%) refluxed in ethanol. The present protocol using aluminium sulfate a mild solid catalyst has several merits, such as low cost, high yield, and shorter reaction time, with no byproducts.

Keywords: Aluminium sulfate, Dimedone, Dihydropyridine, Ethyl acetoacetate Polyhydroquinoline, Four components.

INTRODUCTION

Recently, increased efforts have been focused on the synthesis of 1,4–dihydropyridine compounds due to their significant biological activity [1-5]. For example, dihydropyridine drugs such as nifedipine, nicardipine, amlodipine and others are effective cardiovascular agents for the treatment of hypertension [6, 7]. 4-Aryl-1,4-dihydropyridines have been explored for their calcium channel activity and the heterocyclic rings are found in a variety of bioactive compounds such as vasodilators, bronchodilators, and anti-atherosclerotic, anti-tumor, anti-diabetic, geroprotective and heptaprotective agents [8-11]. Moreover, these compounds can also act as neuroprotectants, platelet anti-aggregators, cerebral anti-ischemic agents and chemosensitizers [12-15]. The remarkably diverse activities of these compounds has attracted many chemists to attempt to synthesize this heterocyclic nucleus.

The classical method for the synthesis of 4-aryl-1,4-dihydropyridine involves mixing aldehyde with ethyl acetoacetate and ammonia in acetic acid or in refluxing alcohol [16]. However, this method has several disadvantages including longer reaction times, the us of an excess amount of organic solvent, lower product yields and harsh refluxing conditions. Since the method of Hantzsch was described more than a use century ago [17-19], several efficient methods have been developed for the synthesis of 1, 4-dihydropyridines that involve the use of a microwave [20-22], ionic liquids [23-24], high temperatures in refluxing solvent [25-35], TMSCl-NaI [36] and metal triflates [37]. However, the use of high temperatures, expensive metal precursors and the resultant longer reaction times limit these methods. 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 room for further improvement, namely using milder reaction conditions and resulting in higher product yields.

Aluminium sulfate, with its mild acidity, involatility and incorrositivity, is insoluble in common organic solvents; therefore, the use of aluminium sulfate in organic synthesis is very limited. Here, we report the use of aluminium sulfate as a catalyst for the multicomponent Hantzsch reaction. Our results demonstrate that aluminium sulfate is a very effective, environmentally friendly catalyst for the four-component condensation of ethyl acetoacetate, diemedone, aromatic aldehyde and ammonium acetate to form a polyhydroquinoline derivative in high yield.

RESULTS AND DISCUSSION

In the initial experiments we screened common Lewis acids for their ability to catalyze the Hantzsch reaction. To study the feasibility of the common Lewis acids, the reaction of ethyl acetoacetate, dimedone, benzaldehyde and ammonium acetate was selected as a model. The common Lewis acids such as silicotungstanic acid, stannous chloride, zinc oxide, ferric sulfate produce low yield. However, among the common Lewis acids studied for this reaction, aluminium sulfate was found to be the most effective catalyst as it resulted in the highest conversion of ethyl acetoacetate into polyhydroquinoline. (Table 1 entry 5).

Table 1 Catalytic activity of soild acid and Lewis acid in Hantzsch reaction[a]

Entry	Catalyst (20%mol)	Time (hs)	%Yield[b]
1	Silicotungstanic acid	5	45
2	Stannous chloride	5	52
3	Zinc oxide	5	60
4	Ferric sulfate	4	65
5	Aluminium sulfate	3	92

a: Reaction conditions ethyl acetoacetate (1mmol), dimedone(1mmol), benzaldehyde (1mmol) and ammonium acetate (1.5mmol) EtOH reflux b: isolated yield

Our initial experiments focused on the optimization of the amount of $Al_2(SO_4)_3$ by using the ratio 1 equivalent of ethyl acetoacetate, 1 equivalent of dimedone, 1 equivalent of benzaldehyde and 1.5 equivalent of ammonium acetate and variable amount of $Al_2(SO_4)_3$. We observed that 20 mole % of $Al_2(SO_4)_3$ could effectively catalyze the reaction and increase the amount of $Al_2(SO_4)_3$ to 30 mol % with no substantial improvement in the yield. (Table 2 entry 1-6) .

Table 2 Synthesis of Polyhydroquinoline derivative under different conditions[a]

Entry	$Al_2(SO_4)_3$ mol %	Time hrs	%Yield[b]
1	No catalyst	24	42
2	5	20	56
3	10	8	75
4	15	6	80
5	20	4	92
6	30	4	93

a: Reaction conditions ethyl acetoacetate (1mmol), dimedone(1mmol), benzaldehyde (1mmol) and ammonium acetate (1.5mmol) EtOH reflux b: isolated yield

In an effort to obtain improved yields, three solvents were screened in the Hantzsch reaction of ethyl acetoacetate, dimedone, benzaldehyde and ammonium acetate at reflux condition and the results are summarized in Table 3. Ethanol provided excellent yields and proved to be the solvent of choice, whereas acetic acid afforded lower yield. The reaction in water afforded very poor yield.

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Table 3 $Al_2(SO_4)_3$ catalyzed Hantzsch reaction in different solvent

Entry	Solvent	%Yield
1	EtOH	92
2	Acetic acid	65
3	Water	25

These results encouraged us to extend this method to synthesize other substituted polyhydroquinoline. All yields were those of isolated products after purification and are comparable to the best overall yields previously reported for the appropriate polyhydroquinoline products. The structures of the products were confirmed from melting point and spectroscopic data.

It follows from Table 4 that yields of all the products are good to excellent and a variety of functionalities such as nitro, halide, ether and hydroxyl can be accommodated in polyhydroquinoline derivatives. Aromatic aldehydes carrying electron withdrawing substituent's reacted in shorter reaction time with excellent yields to give polyhydroquinoline compared to the presence of electron donating groups in aromatic aldehydes.

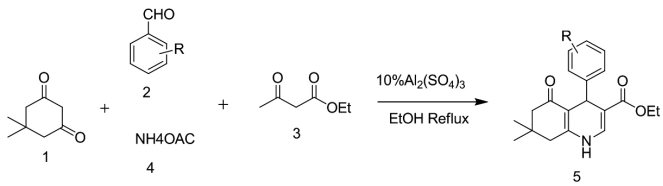

Figure 1 $Al_2(SO_4)_3$ catalyzed synthesis of Polyhydroquinoline derivatives

Table 4 $Al_2(SO_4)_3$ catalyzed synthesis of Polyhydroquinoline derivatives through Hantzsch reaction[a]

Entry	2	Ar	Time (hr)	Product	% Yield	Mp(°C)
1	2a	C_6H_5	4	5a	92	203-205
2	2b	4-$MeOC_6H_4$	5	5b	88	254-256
3	2c	4-HOC_6H_4	3	5c	91	233-236
4	2d	3,4-$(OH)_2C_6H_3$	5	5d	86	248-250
5	2e	2,5-$(OMe)_2C_6H_3$	6	5e	85	158-160
6	2f	3,4,5-$(MeO)_3C_6H_2$	4	5f	89	198-200
7	2g	4-HO-3-CH_3O-C_6H_3	6	5g	87	206-209
8	2h	4-Br C_6H_4	5	5h	89	250-254
9	2i	4-Cl C_6H_4	5	5i	87	230-233
10	2j	4-F C_6H_4	5	5j	91	198-200
11	2k	4-NO_2 C_6H_4	5	5k	91	240-243
12	2l	2-NO_2 C_6H_4	4	5l	83	207-209
13	2m	3,4-$(OMe)_2C_6H_3$	5	5m	89	230-234
14	2n	4-Me C_6H_4	5	5n	86	256-258
15	2o	2-Br C_6H_4	5	5o	79	236-238

a: Reaction conditions ethyl acetoacetate (1mmol), dimedone(1mmol), benzaldehyde (1mmol) and ammonium acetate (1.5mmol), $Al_2(SO_4)_3$ (0.1mmol) EtOH reflux b: isolated yield

Role of aluminium sulfate in this reaction is to activate the aldehyde by binding of aluminium sulfate with the oxygen atom which ultimately enhances the electrophilicity of the aldehyde and leads to a decrease in reaction time.

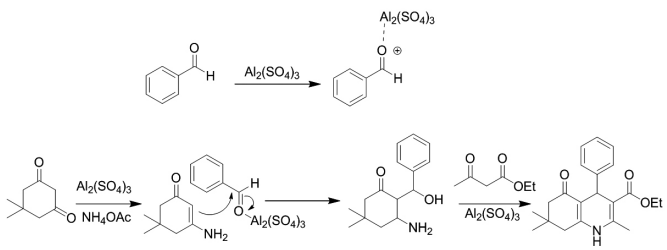

Figure 1: Mechanism of Aluminium Sulfate catalyzed synthesis of Polyhydroquinoline

CONCLUSION

We have described a simple and general method for the synthesis of polyhydroquinoline by using aluminium sulfate a solid acid catalyst, which has many advantages such as inexpensive and easily available, easy to handle, reusability, recovery, insoluble in most organic solvents, being eco-friendly and green process catalysts. The method offers several advantages including high yields, an ecofriendly procedure, shorter reaction times and a simple work-up procedure.

EXPERIMENTAL

General Procedures

Aluminium sulfate is purchased from loba chemicals. All the yields were calculated from crystallized products. Melting points of the compounds were determined in open capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded at room temperature on Bruker AC-250 spectrometers using TMS as internal standard.

General Procedure for the synthesis of polyhydroquinoline

A mixture of dimedone (2mmol), aromatic aldehyde (2mmol),ethyl acetoacetate(2mmol), ammonium acetate (4mmol) and 10% aluminium sulfate was refluxed in ethanol for the time as mentioned in Table 4. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured into crushed ice and the solid product was separated, filtered and recrystallized from ethanol to get pure yellow or white coloured crystalline polyhydroquinoline derivative **5a-5o**.

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