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$Al_2(SO_4)_3$ is an efficient and mild acid catalyst for the one-pot, four-component synthesis of polyhydroquinoline

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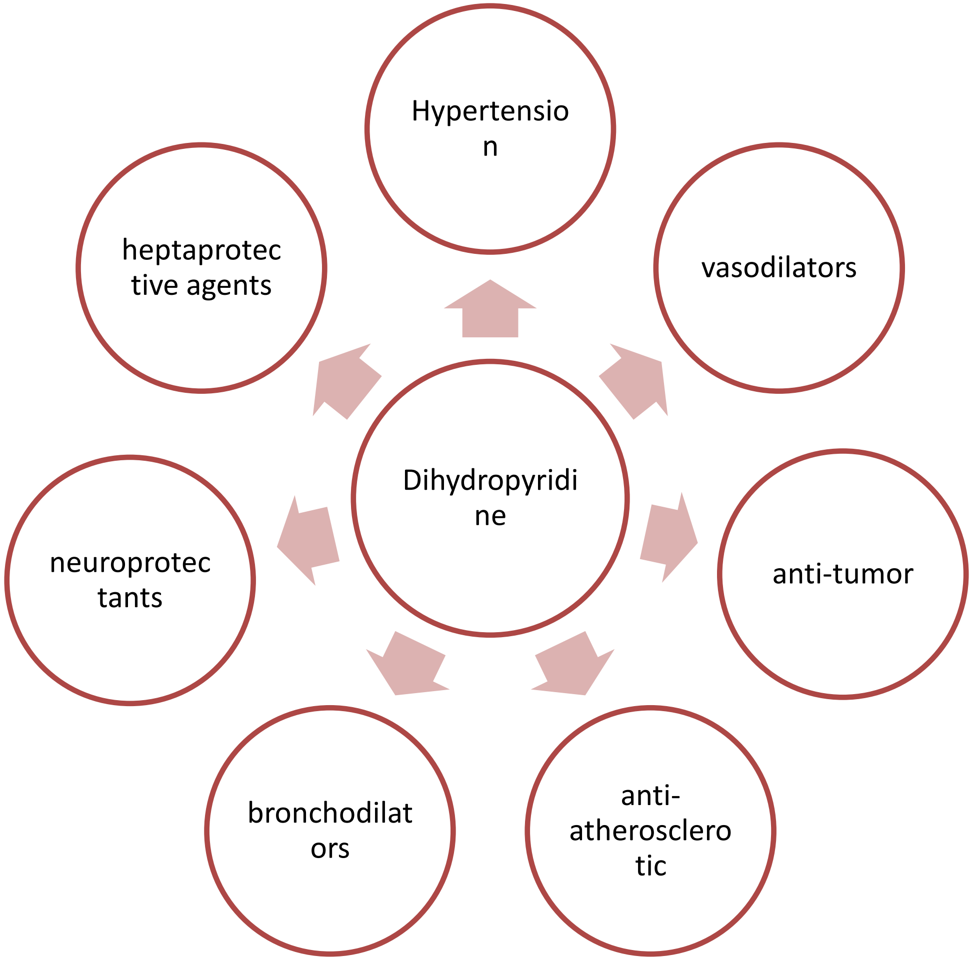
Introduction



Hypertension

vasodilators

anti-tumor

anti-atherosclerotic

bronchodilators

neuroprotectants

heptaprotective agents

Dihydropyridine

Figure 1. Various biological activity of Dihydropyridine

Reported Methods for synthesis of Polyhydroquinoline

- 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. 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 century ago, several efficient methods have been developed for the synthesis of 1, 4-dihydropyridines that involve the use of a microwave ionic liquids, high temperatures in refluxing solvent, TMSCl-NaI and metal triflates. 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

Entry	Catalyst (20% mol)	Time (hs)	% Yield
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

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 Synthesis of Polyhydroquinoline derivative under different conditions

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

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.

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.

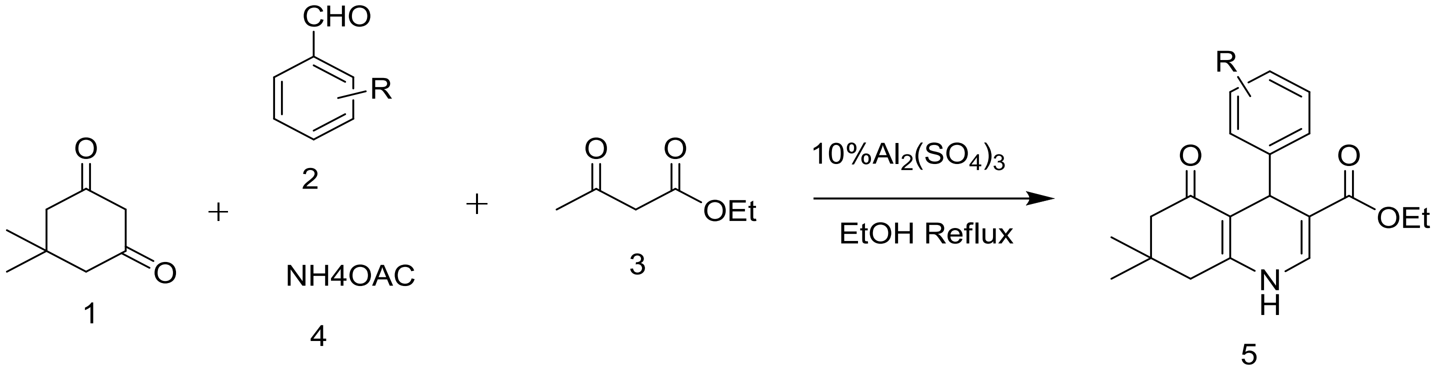


Figure 1 $Al_2(SO_4)_3$ catalyzed synthesis of Polyhydroquinoline derivatives

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

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.