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A Review: Alternative Methods of Preparing 1, 4- Dihydropyridine Derivatives by Hantzsch Reaction

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Abstract: **1, 4-dihydropyridines and its derivatives are an important class of heterocyclic scaffolds of low molecular weight. Dihydropyridines act as calcium-channel blockers. They have been used for the treatment of a variety of cardiovascular diseases due to their potential antihypertensive, anti-angina, vasodilator, and cardiac depressant activities. They show antibacterial, anticancer, anti-leishmanial, anticoagulant, anticonvulsant, anti-tubercular, antioxidant, antiulcer, and neuroprotective properties. The reaction to produce 1, 4-dihydropyridines (1, 4-DHPs) was reported by Arthur Hantzsch. This review article will throw light on some green attempts done to improve the synthesis of 1, 4- Dihydropyridine derivatives via Hantzsch reaction.**

Index Terms: **1, 4-dihydropyridines, Green approach, Hantzsch reaction, one-pot multicomponent reaction, ceric ammonium nitrate.**

I. INTRODUCTION

A century ago, synthesis of 1, 4-dihydropyridines (1, 4-DHPs) was reported by Arthur Hantzsch (Hantzsch, A. & Justus, L. 1882). These have important pharmacological and biological activities, such as antihypertensive, anti-anginal and as calcium channel blocker for cardiovascular disease. Some of the clinically important drugs are available in the market with variable new active functional groups in their main skeleton, such as Nicardipine, Nifedipine, Nimodipine, Felodipine, Isradipine and Amlodipine (Bossert, F. et al., 1981; Love B et al., 1974; Gilpin, P.K. & Pachla, L.A., 1999; Cosconati ,S. et al ., 2007). Many attempts are being made to improve the yield of product synthesised via Hantzsch reaction using different alternative processes (Correa, W.H. & Scott, J.L., 2001; Sapkal, S.B. et al., 2009; Bridgwood, K.L. et al., 2008; Kumar, A. & Maurya ,R.A., 2008; Mirela, F.L. et al., 2008). However, most of these reactions have been reported with new trends as one-pot multicomponent reactions (MCRs) in the last decade. The earlier methods of synthesis were found to have limitations like: longer reaction time, use of costly catalyst, higher temperature and tedious workup procedure. A remarkable variation in MCRs (Kataria ,M et al., 2015; Shen, L., 2009; Patel, H.M. et al., 2017) developed using various ionic liquids as various Lowry-Bronsted acids, with several advantages has been well documented. (Sharma ,S. et al., 2008; Wang, L. et al., 2005; Ko S, Yao C., 2006).

Conventional method of this reaction allows the preparation of dihydropyridine derivatives by condensation of an aldehyde with two equivalents of a β-ketoester in the presence of ammonia. The positive points of the Hantzsch pyridine synthesis are lesser reaction times, simplicity of the reaction, good yield of product and easy workup procedures.

II. EXPERIMENTAL DETAILS OF ALTERNATIVE METHODS

Scientists have been carrying out Hantzsch reactions by varying the reaction conditions and making the procedure greener. A few of the novel, clean and green synthesis have been reported here.

A. Synthesis of 1,4- dihydropyridines with Ceric Ammonium Nitrate (CAN) as Catalyst

Sharma, M. G. et al (2017) have carried out a greener procedure i.e. one pot multicomponent synthesis of dihydropyridine derivatives using the CAN as the catalyst without using any solvent. They took all reactants together and stirred the reaction mixture for 1–2.5 h at room temperature (Scheme 1). The reaction was monitored by TLC. The product

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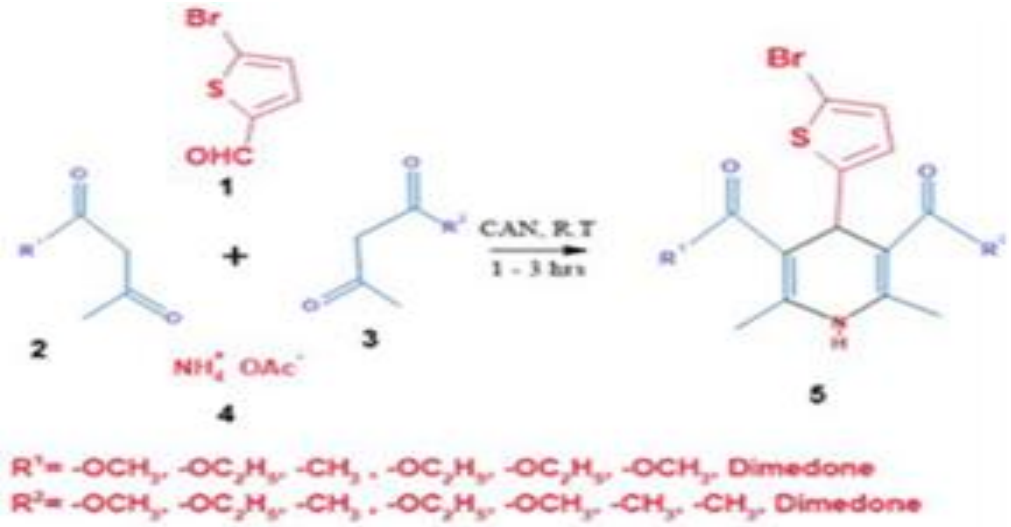


Scheme 1. Synthesis of 1,4- dihydropyridines with Ceric Ammonium Nitrate (CAN) as Catalyst

was purified using *n*-hexane and recrystallized using ethanol followed by charcoal treatment.

The result highlighted that this procedure was more efficient than the conventional method. The interesting finding of this work was that the compounds obtained showed excellent antibacterial activity and were found highly active against *S. aureus* and *B. subtillus* compared with the standard drug Ampicillin, [Sharma, M. G., Rajani et al (2017)].

B. Method to carry out One- pot Hantzsch reaction in aqueous medium

Number of synthesis (Saha, M. et al., 2008; Goswarmi, P., 2009; Tamaddon, F., et al., 2011; Palmisano, G. et al., 2011; Safari, J. et al., 2011); Kumar, A. & Sharma, S., 2011) have been reported using eco-friendly processes like - using aqueous medium, without the use of catalyst and microwave synthesis.

It has been observed that the reactions carried in open-vessel (typically, the flask charged with a reflux condenser) resulted in lesser efficiency and lower yields whereas when Hantzsch reaction was carried out in a sealed vessel using aqueous medium with stoichiometric amount of reactants, a very high efficiency and excellent yields were obtained (Fig. 1, Table I & Table II).

This reaction is Catalyst free, organic solvent- free, and

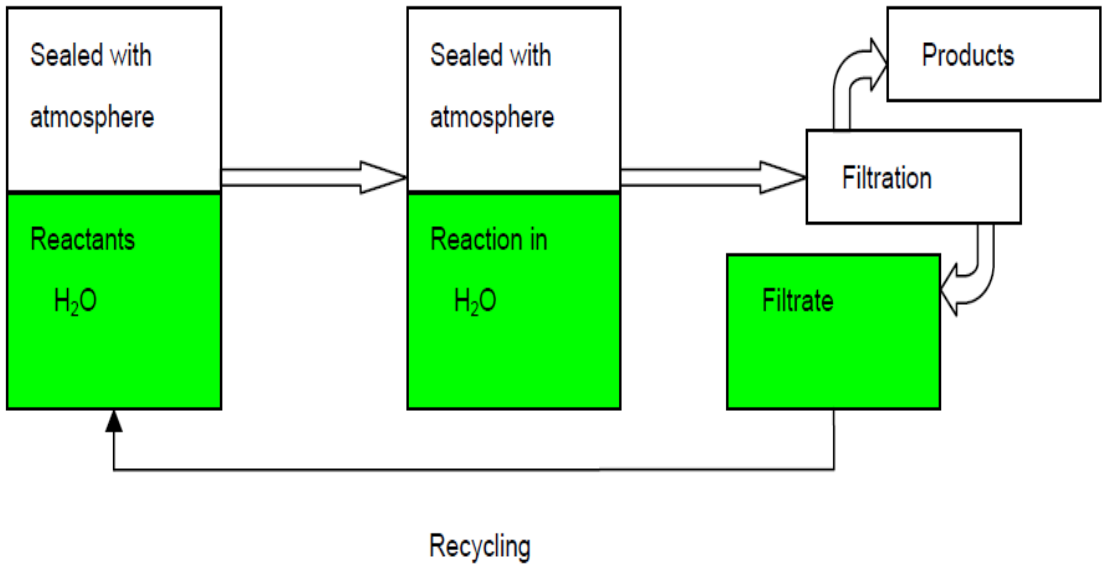
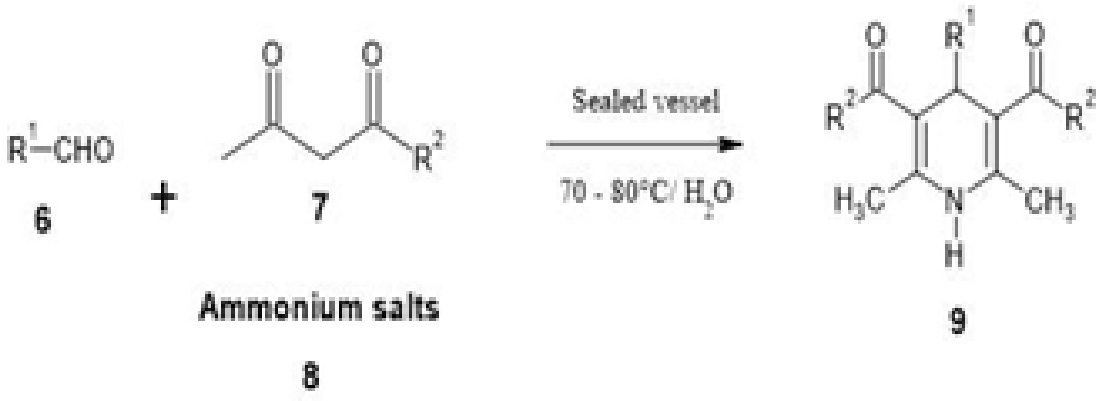


Fig. 1. Flow Chart of Hantzsch Reaction in a Sealed Vessel using aqueous medium



Scheme 2. Hantzsch Synthesis in a sealed vessel using aqueous medium

condenser-free clean procedure and was accomplished smoothly in the sealed system (Scheme 2). This procedure established has the advantages of least leaks and emission, high efficiency and recyclable performance, which has the potential application for the green synthesis (Yang J., et al., 2013).

Table I. Comparison of yields for different aldehydes

Sr. No.	R_1	R_2	Time (h)	%Yield
1	4-$OCH_3C_6H_4$	OEt	1	96
2	4-$CH_3C_6H_4$	OEt	1	92
3	C_6H_5	OEt	1	96
4	4-ClC_6H_4	OEt	1	95
5	3-ClC_6H_4	OEt	1	91
6	4-$CH_3C_6H_4$	OMe	1	94
7	3-$NO_2C_6H_4$	OMe	1	95
8	C_6H_5	OMe	1	95

Table II. Optimization of temperature & open or sealed conditions for higher yield

Sr. No.	Reaction system	Time (h)	Temp ^{0}C	% yield
1	Open	3.5	50- 60	76
2	Open	2	70-75	82
3	Sealed with air	1	70-75	96
4	Sealed with CO_2	1	70-75	91

C. Method to carry out One- pot Hantzsch reaction in aqueous medium

1) Procedure using Carbon Nanotube for Synthesis of 1,4-dihydropyridines

Reactants were taken along with 0.001 gr of aminated carbon nanotubes as catalyst in ethanol and stirred (Fig. 2 & Scheme 3). Progress of the reaction was monitored by TLC. Final product obtained was purified and recrystallised. High yield of DHP's was obtained showing high efficiency of carbon nanotubes catalyst. Hence it can be very effective for large scale synthesis. Also, it has added advantage that the catalyst can be reused many times.

Reactions were carried out with different solvents like acetonitrile ethanol, lime water, water mixture, etc. and in solvent free environment. It was proved that best yield was obtained using alcohol and 85ºC temperature.

Experiments have proved that this method has some additional advantages such as the procedure is very simple and workup is easy, new recyclable catalyst is used, and products are obtained in high yield.

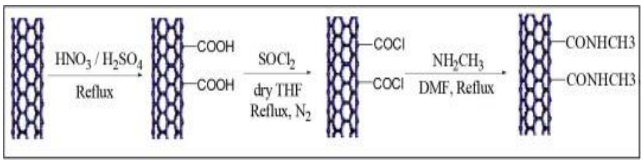
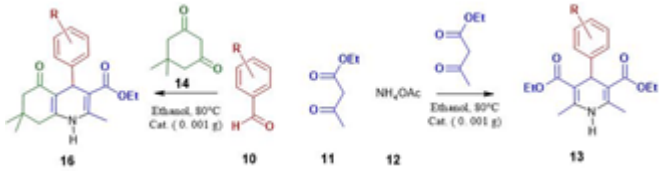


Fig. 2. Preparation of aminated Carbon Nanotubes as Catalyst



Scheme 3. Hantzsch Synthesis in Aminated Carbon Nanotubes as Catalyst in Ethanol

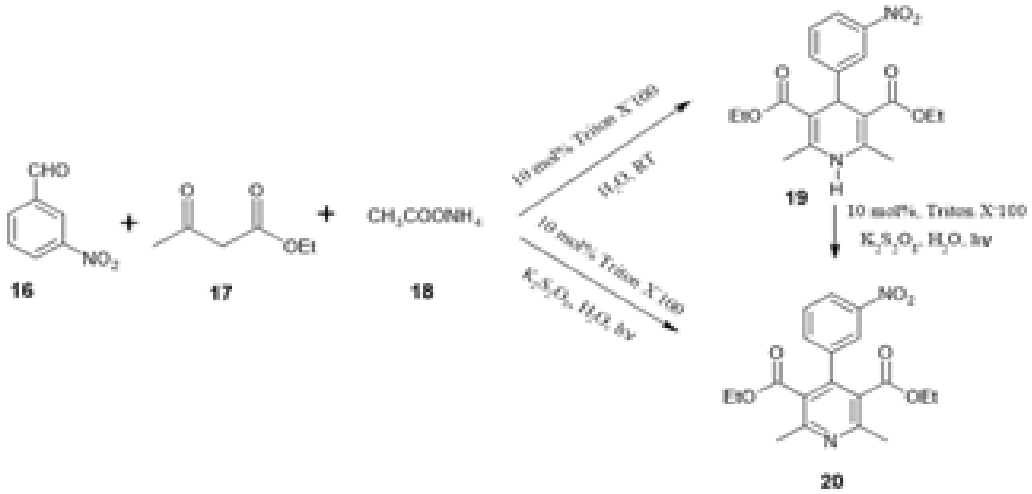
Roya Mahinpoura et al. (2017) in the study of antimicrobial activity revealed that all compounds synthesised by above method had antibacterial activity against gram positive bacteria and are effective against fungi in addition to gram positive bacteria.

D. Microwave Assisted Synthesis

Nowadays, microwave has been extensively used in synthesis of 1, 4-DHP's to reduce reaction time and to get higher efficiency. Studies have shown 1, 4- DHP's have been prepared both in dry media as well as using aqueous solvents. Eynde, J. J. V., and Mayence, A. (2003) have shown that the use of the toxic reagents and organic solvents was reduced and DHP's were successfully prepared in good yields when reaction was carried out in microwave in the presence of ammonium formate. The problem of disposal was also reduced as no inorganic support was used. Thus, good yield of the products with minimum loss of energy in solvent free condition was obtained by eco-friendly greener method (Jacques J., et al., 2003).

class of pharmacologically active drugs. Various attempts have been made to make synthesis greener by changing the catalyst, solvents and procedures and to increase the yield, purity and activity of the products.

Some of the attempts such as using CAN catalyst without solvent were greener and the product was having improved antibacterial properties. Use of recyclable catalyst such as multiwalled carbon nanotube was little more time consuming but optimization of conditions of temperature gave better yields. In recent advances, it is observed that the use of non-ionic surfactant triton 100 for synthesis of 1, 4- dihydropyridine gave 100% yield in aqueous medium at room temperature in visible light.



Scheme 3. Synthesis of 1,4- dihydropyridine derivatives in presence of $K_2S_2O_8$ & Triton X-100 at room temperature & in presence of visible light

E. Synthesis of 1,4- dihydropyridine in non- ionic surfactant Triton X-100, in an aqueous medium at room temperature in visible light

Ghosh, et al., (2013) developed eco-friendly way for synthesis of 1,4-dihydropyridine derivatives by the oxidation using a one pot synthesis where reactants were irradiated with potassium persulphate in the presence of visible light in aqueous micellar medium and almost 100% yields were obtained in very short span of time (Scheme 4). It was observed that during the reaction there was the formation of micelles, or micelle-like colloidal aggregates, from the non-ionic surfactant and the reaction mixture in water, measured by dynamic light scattering and seen through an optical microscope. This process has advantage as ammonia is generated in neutral conditions and purification is easier.

CONCLUSION

Hantzsch reaction plays an extensive role in synthesis of 1, 4-dihydropyridines which are considered as one of the important

REFERENCES

Bossert, F., Meyer, H. & Wehinger, E. (1981). 4-Aryldihydropyridines, a new class of highly active calcium antagonists. Angewadte Chemie Journal of the German Chemical society, 20, 762–769.

Bridgwood, K.L., Veitch, G.E. & Ley, S.V. (2008). Magnesium nitride as a convenient source of ammonia: preparation of dihydropyridines. Organic Letters 10, 3627–3629.

Correa, W.H. & Scott, J.L. (2001). Solvent-free, two-step synthesis of some unsymmetrical 4-aryl-1, 4-dihydropyridines. Green Chemistry 3, 296–301

Cosconati, S., Marinelli ,L., Lavecchia, A. & Novellino, E. (2007). Characterizing the 1, 4-dihydropyridines binding interactions in the L-Type Ca2+ channel: model construction and docking calculations. Journal of Medicinal Chemistry 50, 1504–1513.

Ghosh,P.P, Mukherjee,P. & Das, A.D(2013). Triton-X-100 catalyzed synthesis of 1,4-dihydropyridines and their aromatization to pyridines and a new one pot synthesis of

pyridines using visible light in aqueous media†. Royal Society of Chemistry 8, 381-391

Gilpin, P.K. & Pachla, L.A. (1999) Pharmaceuticals and related drugs. Analytical Chemistry 71, 217–233.

Goswarmi, P. (2009) One pot synthesis of unsymmetrical dihydropyridines by green, catalyst free and environmentally benign protocol. Green Chemistry Letters and Reviews 1:173-177.

Hantzsch, A. & Justus, L. (1882) On the synthesis of pyridine-like compounds from aceto acetic ether and aldehyde ammonia Annalen der Chemie. 215, 1–82.

Jacques, J., Eynde, V. & Mayence, A. (2003) Synthesis and Aromatization of Hantzsch 1, 4-Dihydropyridines under Microwave Irradiation. An Overview Molecules 8, 381-391

Kataria ,M., Pramanik, S , Kumar, M. & Bhalla, V.(2015). One-pot multicomponent synthesis of tetrahydropyridines promoted by luminescent ZnO nanoparticles supported by the aggregates of 6,6-dicyanopentafulvene. Chemical Communications (Cambridge). 51, 1483–1486.

Ko S, Yao C. (2006) Ceric ammonium nitrate (CAN) catalyzes the one-pot synthesis of polyhydroquinoline via the Hantzsch reaction. Tetrahedron 62, 7293–7299.

Kumar, A. & Maurya, R. A. (2008) Efficient synthesis of Hantzsch esters and polhydroquinoline derivatives in aqueous micelles. Synlett 6, 883–885.

Kumar, A. & Sharma, S. (2011) A grinding-induced catalyst- and solvent-free synthesis of highly functionalized 1,4-dihydropyridines via a domino multicomponent reaction. Green Chemistry 13:2017-2020.

Love B, Goodman M, Snader KM, Tedeschi R, Macko E. (1974). Hantzsch-type dihydropyridine hypotensive agents. Journal of Medicinal Chemistry17, 956–965.

Mahinpour, R. Moradi, L.,Zahraei, Z. & Pahlevanzadeh, N (2017) New synthetic method for the synthesis of 1,4-dihydropyridine using aminated multiwalled carbon nanotubes as high efficient catalyst and investigation of their antimicrobial properties Journal of Saudi Chemical Society 11.,001,21-23

Mirela, F.L., Mladen, L. & Vladimir, V. (2008). An efficient, metal-free, room temperature aromatization of Hantzsch1,4-dihydropyridines with urea–hydrogen peroxide adduct, catalysed by molecular iodine. Tetrahedron 64, 5649–5656.

Palmisano, G., Tibiletti, F.& Penoni, A.(2011) Colombo F, Tollari S, Garella D, Taglipeitra S, Cravotto G. Ultrasound-enhanced one-pot synthesis of 3-(Het) arylmethyl-4-hydroxycoumarins in water. Ultrasonics Sonochemistry 18(2):652-660.

Patel, H. M., Patel, K.D. & Patel, H.D.(2017). Facile synthesis and biological evaluation of New Mannich products as potential antibacterial, antifungal and antituberculosis agents: molecular docking study. Current Bioactive Compounds. 13, 47–58

Safari, J.,Banitaba S.H.& Khalili ,S.D. (2011) Cellulose sulfuric acid catalyzed multicomponent reaction for efficient synthesis of 1,4-dihydropyridines via unsymmetrical Hantzsch reaction in aqueous media. Journal of Molecular Catalysis A: Chem. 335(12):46-50.

Saha, M., Roy, S., Chaudhuri, S.K. & Bhar, S. (2008) Microwaveassisted ammonium formate-mediated synthesis of Hanstzch dihydropyridines under solvent-free conditions a green protocol. Green Chemistry Letters and Reviews 2008;1:99102

Sapkal. S.B, Shelke, K.F.B, Shingate, B., Shingare, M.S (2009). Nickel nanoparticle-catalyzed facile and efficient one-pot synthesis of polyhydroquinoline derivatives via Hantzsch condensation under solvent-free conditions. Tetrahedron Letters 50, 1754–1756

Sharma, M.G., Rajani, D. P. & Patel, H. M. (2017) Green approach for synthesis of bioactive Hantzsch 1,4-dihydropyridine derivatives based on thiophene moiety via multicomponent reaction Royal Society Open Science 4, 170006

Sharma, S., Hazarika, D. & Konwar, P.D.(2008). A simple, green and one-pot four-component synthesis of 1, 4-dihydropyridines and their aromatization. Catalysis Communications. 9, 709–714

Shen, L., Cao, S., Wu, J., Zhang, J., Li, H., Liu,N. & Qian ,X. (2009) A revisit to the Hantzsch reaction: unexpected products beyond 1,4-dihydropyridines. Green Chemistry 11, 1414–1420.

Tamaddon, F., Razmi, Z. & Jafari ,AA.(2011) Synthesis of 3,4-dihydropyrimidin-2(1H)-ones and 1,4-dihydropyridines using ammonium carbonate in water. Tetrahedron Letters 51(8):1187-1189.

Wang, L., Sheng, J., Zhang, L., Han, J., Fan, Z. & Tian, H. (2005). Facile Yb(OTf)3 promoted one-pot synthesis of polyhydroquinoline derivatives through Hantzsch reaction. Tetrahedron 61, 1539–1543.

Yang,J. , Jiang, C., Yang , J., Qian, C & Fang, D (2013) A clean procedure for the synthesis of 1,4-dihydropyridines via Hantzsch reaction in water, Green Chemistry Letters and Reviews, 6:3, 262-267

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