Synthesis of Hantzsch Dihydropiridine Using Water as Solvent, A Green Approach

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Dihydropyridines had been known and proved to be an extremely important molecule with pharmaceutical importance from last few decades. With proper structural modification this compound can be successfully used to get desired result as bioactive molecules. In the present review focus will be given on the synthesis of 1,4 Dihydropyridine derivatives having structural diversity in aqueous medium. Along with the other conventional as well as nonconventional methods, synthesis of 1,4 Hihydropyridine in aqueous medium is also attracting immense interest among the researchers'. Water in present time is being extensively researched as a green solvent. Many organic reactions using water as solvent are much acceptable in present time not only because water is most abundant solvent on earth, but also it has unique selectivity and reactivity compared to other conventional organic solvents. Hantzsch Dihydropyridine synthesis using water as solvent can be carried out in moderate temperature with good to satisfactory yield. In this point it is worth mentioning that all of the following multicomponent reactions have fulfilled many of the conditions mentioned in the twelve principles of green chemistry.
Keywords: Hantzsch Dihydropyridine, Green Chemistry, Aqueous medium.

Introduction:

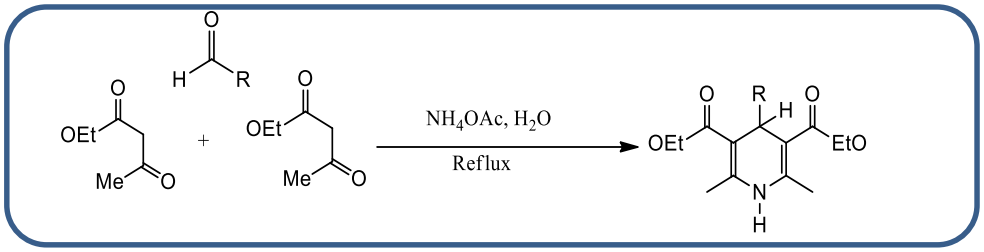
Synthesis of different bio-active molecules is of great demand in the field of pharmaceutical industry. Different heterocyclic molecules are the useful synthons for the preparation of these types of bioactive molecules. Differently substituted 1,4-dihydropyridines are useful molecules as they are used in the treatment of Alzheimer's disease[1]. Hantzsch Dihydropiridines are also known to be efficient Ca^{+2} channel blocker. So they are used in the cardiovascular disorder and hypertension[2]. Not only that, these compounds can also be used as synthetic intermediates of different pyridine derivatives by means of oxidative aromatization[3a-b]. Different synthetic protocols using ammonia[4a], N-(1-chloroalkyl)-pyridinium chloride[4b], refluxing ammonium hydroxide in a closed vessel microwave synthesizer[4c], urea silica gel[4d], ammonium acetate in ethanol under microwave irradiation[4e], potassium fluoride alumina[4f], ammonium acetate under conventional heating[4g], 2,4,6-trichloro 1,3,5-triazine[4h], and many others are reported in literature.

But most often the reactions reported in different literatures are carried out in different organic solvents. This leads to a serious threat for environmental hazard. Though several solvent-free protocols[4d,4f] have also been developed for this multicomponent reaction, but the requirement of toxic organic solvents can't still be avoided as during the product isolation process and purification process. In course of these product isolation and purification process huge exposure of organic solvent cannot be omitted. As a result, the use of organic solvent had been an integral part in synthetic chemistry for long time. And this unavoidable need of specific solvent for a desired reaction has economical, environmental, and social impact in its worse side. This drives researchers to develop alternative methods for organic transformations where to some extent the use of these toxic reagents and organic solvents can be minimized.

Thus, from last few decades' innovations in the field of developing newer strategies in multicomponent reactions with greener protocols have drawn much interest, especially in case of organic synthesis, and other synthetic areas with greener approach. The present review will summarise the advances in the formation of various Dihydropyridine frameworks using the multicomponent reaction strategy by using aqueous medium as a green solvent.

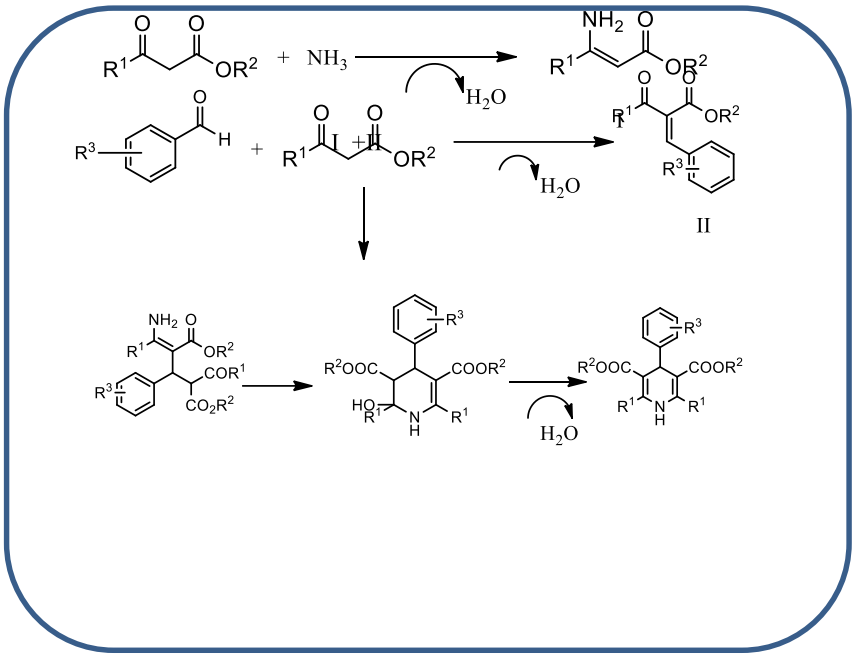
SYNTHESIS OF DIHYDROPYRIDINE IN AQUEOUS MEDIUM

Arthur R, Hantzsch in 1881 first reported[5] a nitrogen based six membered heterocyclic compound, the dihydropyridine, which was later named after his name Hantzsch Dihydrpyridin. This molecule was synthesised through a one-pot reaction of two molecules of ethyl acetoacetate, a carbonyl compound and a source of nitrogen (especially ammonia or ammonium acetate) (Scheme 1). Soon after the report gets published, interest was developed among the synthetic chemists. And thereafter many developments were done. Moreover, the synthetic applications and medicinal importance of this molecule encouraged the researchers to find newer developments.



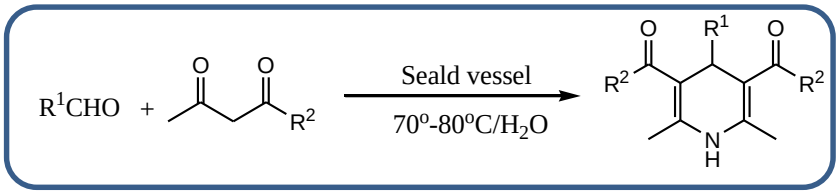
SCHEME: 1, Synthesis of Dihydropyridine.in aqueous medium

Almost a century later in 1986 Kartrinsky and co-workers[6] had suggested a mechanistic pathway for the reaction. The mechanism involves the formation of an enamine (I) and a Chalcone (II) as intermediate. Later through a cyclization reaction Dihydropyridine is formed (Scheme 2).



SCHEME: 2, Mechanistic pathway for the synthesis of Hantzsch Dihydropyridine

Water being the most abundant in nature and environmental friendly solvent, it works best for biochemical processes. If the cost and safety are concerned, it can be supposed to be the most desirable and effective solvent for in vitro chemical reactions. Nowadays researchers are much interested in the study of different organic reactions using water as solvent[7a-h]. After the remarkable study and inspiring publication by Sharpless and co-workers[8] regarding cycloaddition reaction in water medium, various new organic synthesises and their applications in water medium have been reported[9a,b]. As a part of this study Dong Fang and co-workers have introduced a new method for synthesis of 1,4 dihydropyridine by a clean process using water as solvent. This one pot synthesis of 1,4 Dihydropyridine was performed in aqueous medium without using any solvent or even without any catalyst. The reaction was carried out in a closed vessel in air, steam or nitrogen atmosphere to get excellent yield with good purity (Scheme-3). A comparative study using open and sealed vessel shows that reaction in the sealed vessel has higher efficiency and better yield (table-1).



Scheme: 3 Synthesis of DHP in sealed vessel

Table-1: Effect of different reaction systems

Entry	Reaction System	Reaction time (h)	Temperature (ºC)	Yield (%)
1	Open	3.5	55-60	67
2	Sealed with air	1	70-75	96
3	Sealed with steam	1	70- 75	96
4	Sealed with nitrogen	1	70-75	96

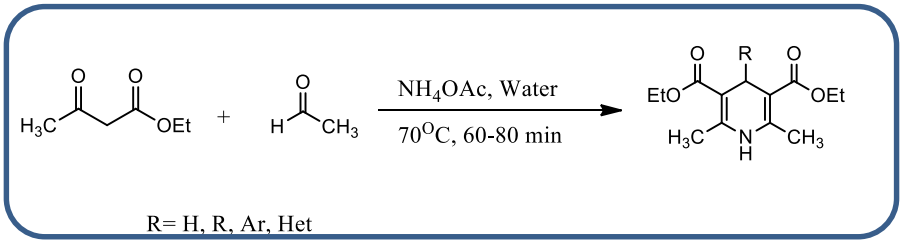
Effect of different solvents in the said reaction were examined by performing the reaction in various solvents (table 2). As seen from Table 2 it is evident that the yield is good to excellent when polar solvents like ethanol or water has been used. Whereas, in case of less polar solvents like Toluene, DCM etc the efficiency as well as the yield were less. This might be due the fact that less solubility of the inorganic ammonium salt in less polar solvents.

Table 2: Effect of different solvents in open vessel

Entry	Solvent	Time (h)	Temperature (^{O}C)	Yield (%)
1	DCM	6	70-75	56
2	Toluene	6	Reflux	33
3	Ethanol	2	70- 75	82
4	Water	2	70-75	72

Reaction conditions: (aldehyde): (b-keto esters): (ammonium carbonate) 1:2:1, open system

As a part of our detailed Study about the synthesis of Hantzsch Dihydropyridine we also reported an ammonium acetate-mediated, catalyst-free synthesis of Hantzsch dihydropyridines using water as solvent[4i] (Scheme-4) which is basically modified development of another report published earlier from our laboratory[4j]. In case of Microwave-assisted ammonium format-mediated synthesis of Hantzsch dihydropyridines under solvent-free conditions[4j] reaction is extremely rapid but the work up procedure is not completely free from the use of organic solvent. The crude product in this Microwave-assisted protocol is gummy semi solid type, which needs precipitation and crystallization procedure using ethanol and crushed ice. Product isolation is even more difficult in those cases where the substrates are long chain aliphatic aldehydes which are susceptible to polymerise under microwave irradiation. On the contrary in the 'On water' protocol[4i] the product isolation is much easier. Simply adding little ethanol and crushed ice on reaction mixture crystalized product is precipitated out in extremely pure form. So this cost-effective and ecofriendly methodology for the synthesis of 1,4, Dihidropyridine is very useful from the green chemistry point of view.



Scheme 4: Catalyst-free synthesis of Hantzsch dihydropyridines in water

The important outcome in the said methodology is that the only two by-products produced are water and acetic acid which are environmentally benign and safe for disposal. In comparison to the by-products obtained in other alternative methods, this protocol eliminates the inorganic solid support and toxic organic solvents. Moreover, unlike the other alternatives there is no requirement of any auxiliary reagents like catalysts in this protocol. Thereby the

separation procedure of the crude product from the catalyst and subsequent purification steps could easily be eliminated. So the disposal of the leftover of the auxiliary is no more a matter of concern. Thus this simplified technique become cost effective as well as time saving. The combination of the 1:1 ethanol water mixture had also been studied as reaction medium. But most of the aryl aldehydes produce lesser yield and some unidentified by-products in this case. Although few alkyl aldehydes compared to the aryl aldehydes responded well in a 1:1 Ethanol water combination.

Conclusion

The comprehensive use of toxic organic solvents and harmful chemical is becoming a great threat for the ecosystem. So the development of new sustainable methodologies is in high demand in industries for the production of scaffolds in terms of drugs agrochemicals etc. Thus with the increase of unconventional techniques like microwave irradiation, ultrasound etc, use of safer auxiliary and green solvents are also becoming popular among the industries as well as in academia. So in terms of increasing the credentials of Green Chemistry these popularized protocols can reduce the environmental impacts and improve the effectiveness. In the present time the use of aqueous medium in organic synthesis is in high demand. Undoubtedly this should be a prime choice for the researchers to use water as green solvent in industries as well as in academic researches. In this chapter a brief overview of the synthesis of Hantzsch Dihydropyridine with structural diversity using water as a prime choice as 'Green solvent' is given.

Considering the importance of Green Chemistry, the present review successfully highlights on all the twelve principles.[10] There is no doubt that the development of green chemistry will surely play significant role in the sustainability of our society. Therefore, further developments of alternative green and facile protocols are anticipated in future. And hopefully, this review article will surely encourage and motivate researchers to design more benign, simpler, cost-effective and efficient approaches for sustainable chemistry.

References

(1) Mauzeral, D.; Westheimer, F.H. *J. Am. Chem. Soc.* **1955**, 77, 2261-2264.

(2) Bossert, F.; Meyer, H.; Wehinger, E. *Angew. Chem. Int. Ed. Engl*. **1981**, 20, 762-769.

(3) (a) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Synthesis*. **2004**, 1015-1020; (b) Han, B.; Liu, Z.; Liu, Q.; Mu, R.; Zhang, W.; Liu Z.-L.; Yu, W. *Synlett* **2005**, 2333-2334.

4) (a) McKillop, A.; Boulton, A.J. *In Comprehensive Heterocyclic Chemistr*y; Katritzky, A.R., Ed.; Vol. 2; Pergamon Press: UK, **1984**; 87-88; (b) Eynde, J. J.; D'Orazio, V.; Mayence, A.; Maquestiau, A. *Tetrahedron* **1992**, 48, 1263-1268; (c) Ohberg, L.; Westman, J. *Synlett*. **2001**, 1296-1298; (d) Yadav, J.S.; Subba Reddy B.V.; Thirupati, P. *Synth. Commun*. **2001**, 31, 425-430; (e) Anniyappam, M.; Murlidharan, D.; Perumal, P.T. *Synth. Commun*. **2002**, 32, 659-663; (f) Aydim, F.; Ozen, R. *J. Org. Chem*. **2004**, 69, 486-487; (g) Zolfigol, M.A.; Safaiee, M. *Synlett*. **2004**, 827-828; (h) Sharma, G.V.M.; Reddy, K.L.; Lakshmi, P.S.; Krishna, P.R. *Synthesis* **2006**, 55-58; (i) Amit Pramanik, Manabendra Saha and Sanjay Bhar. *ISRN Organic Chemistry*, **2012**, Article ID 342738. (j) Manabendra Saha, Sanchita Roy, Subrata Kumar Chaudhuri and Sanjay Bhar. *Green Chemistry Letters and Reviews*. **2008.** 1(2), 99-102.

5) Hantzsch, A. *Chemische Berichte*, **1881**, 14 (14), 1637-1638.

6) Katrinsky, A. R., Ostercamp, D. L., and Yousaf, T. I. *Tetrahedron*. **1986**, 42, 5729–5738.

7) a) R. Breslow, *Accounts of Chemical Research*, **1991**, 24 (6), 159–164. [b] J. B. F. N. Engberts and M. J. Blandamer, *Chemical Communications*, **2001**, 18, 1701–1708. [c] S. Mecking, A. Held, and F. M. Bauers, *Angewandte Chemie International Edition*, **2002**, 41(4), 544–561. [d] N. E. Leadbeater and M. Marco, *Journal of Organic Chemistry*, **2003**, 68(3), 888– 892. [e] K. Yamaguchi, M. Matsushita, and N. Mizuno, *Angewandte Chemie International Edition*, **2004**, 43(12), 1576–1580. [f] S. Minakata, D. Kano, Y. Oderaotoshi, and M. Komatsu, *Angewandte Chemie International Edition*, **2004**, 43(1), 79–81. [g] N. E. Leadbeater, *Chemical Communications*, **2005**, 23, 2881– 2902. h) Biswajit Panda. *ChemSpider Synthetic pages*, **2008**, 267

8) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, and K. B. Sharpless, *Angewandte Chemie International Edition*, **2005**, 44(21), 3275–3279.

9) a) N. E. Leadbeater, *Chemical Communications*, **2005**, 23. 2881– 2902. b) H. Buchammagari, Y.

10) Paul T. Anastas and John C. Warner. *Green Chemistry Theory and Practice*, Oxford University Press. 2000.