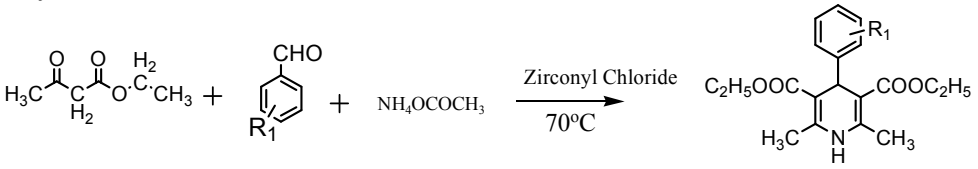
Heterocyclic Letters
Vol. 6| No.4 |709-715|Aug-Oct| 2016
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

EFFICIENT PROCEDURE FOR SYNTHESIS OF 1,4-DIHYDROPYRIDINES UNDER GREEN CHEMISTRY CONDITIONS

Sharda Goel*, Vijender Goel and Anju Bajwan

Department of Chemistry
Maharshi Dayanand University, Rohtak, Haryana
Email: vkg108@gmail.com

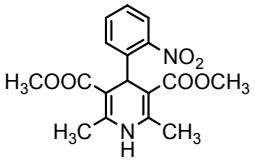
ABSTRACT
A simple, efficient and economic multicomponent reaction for synthesis of various 1,4-dihydropyridine derivatives from an aryl aldehyde, ethylacetoacetate and ammonium acetate using Zirconyl chloride as catalyst avoiding the use of any organic solvent at mild conditions in the absence of any other co-catalyst is illustrated. The process is straightforward, environmentally benign and easily leads to the synthesis of desired product. The catalyst is easily available and inexpensive. This method proves to be advantageous in terms of excellent yield and short reaction time.



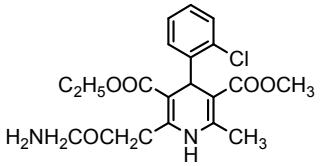
KEYWORDS—Solvent free conditions, 1,4-Dihydropyridines, Hantzsch method, Green Chemistry.

INTRODUCTION
Nowadays, environmental concern is precisely the most important issue so a great emphasis is being laid on the employment of green chemistry technological procedures for synthesis of organic compounds [i]. Synthesis of 1,4-dihydropyridines is a keen area for researchers and attracts more attention due to their noteworthy medicinal applications and biological activities [ii]. 1,4-Dihydropyridines and other related derivatives, act as analogues of NADH coenzymes, as calcium channel blockers [iii], posses remarkable potential as neuroprotectant, neuropeptide [iv] and antitubercular agents [v]. They are used for the treatment of cardiovascular disorder including hypertension, angina, as cerebral antiischemic agents in the treatment of Alzheimer's disease and as a chemosensitizer [vi-vii]. They exhibits significant role as important intermediates in the pharmaceutical (as antimalarial, vasodilator, anesthetic and anticonvulsant), dye and photo industries [viii-ix]. These days

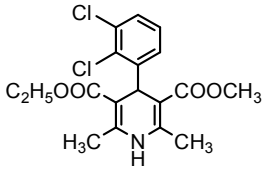
commercial representatives, such as nifedipine (a), amlodipine (b) and felodipine (c) are some of the best selling drugs that are used in the treatment of hypertension.



(a)



(b)



(c)

The classical method for synthesis of 1,4-dihydropyridines by Hantzsch method was known which involves a multicomponent condensation of an aldehyde with ethylacetoacetate and ammonia at room temperature using acetic acid or by refluxing in an alcohol for long time [x]. Numerous modified methods under improved conditions have been reported for synthesis of corresponding 1,4-dihydropyridines, but inspite of their utilities, many of those methods suffer from unsatisfactory yields, toxic reagents, long reaction times and harsh reaction conditions [xi]. As a consequence, the development of an efficient and versatile method for the preparation of 1,4-DHPs is an active ongoing research area and there is still a scope for further improvement towards milder reaction conditions, short reaction times and improved yields.

Zirconyl chloride is one of the few acids that are solid and hence conveniently weighed. Also, unlike some of the strong mineral acids, e.g. nitric acid, sulfuric acid and perchloric acid, it is non-corrosive and non-oxidising. In the present study, it has been seen that Zirconyl chloride can be used for an efficient synthesis of a wide variety of 1,4-DHPs under solvent-free condition in the absence of any other organic or inorganic co-catalyst.

EXPERIMENTAL

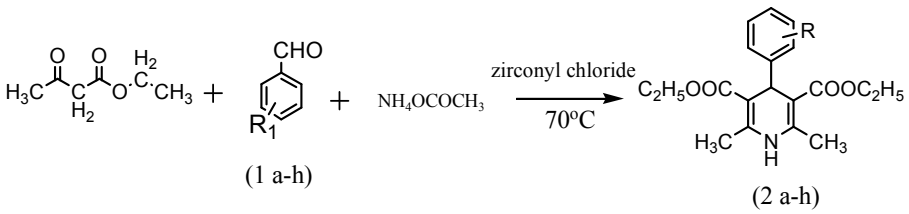
Chemicals were purchased from Merck, Fluka and Aldrich chemical companies. All of the products were identified by comparison of their physical and spectral data with those of the authentic samples. Melting points were determined using an Electrothermal apparatus and were uncorrected. The progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel plates. IR spectra (KBr disc) were recorded on a Perkin Elmer FT-IR-spectrophotometer. ^{1}H NMR spectra (in $CDCl_3$) were obtained by Bruker 400 Ultrasheild (400 MHz) spectrometer.

General Procedure for Preparation of 1,4-Dihydropyridines

A mixture of aryl aldehyde (1 mmol), ethylacetoacetate (2 mmol) and ammonium acetate (1.5 mmol) was heated at 70ºC in the presence of Zirconyl chloride (250 mg) under stirring for 30-65 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and then ethylacetate (5 ml) was added to the reaction mixture. The resulting solid product was filtered and recrystallised from ethylacetate to give a pure product in 60-90 % yield.

RESULTS AND DISCUSSION

In this study, it was directed to explore the development and improvement of new synthetic methodologies for the synthesis of of 1,4-dihydropyridine derivatives from aryl aldehydes, ethylacetoacetate and ammonium acetate using Zirconyl chloride as a catalyst under mild and green reaction conditions as outlined in Scheme 1.



(1 a-h) (2 a-h)

Scheme 1.

A variety of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridines-3,5-dicarboxylate were synthesized from a combination of different aryl aldehydes, ethylacetoacetate and ammonium acetate in 1:2:1.5 ratio under solvent-free conditions. The reactions were completed within 30–65 minutes at 70°C and the products were obtained via filtration and recrystallisation by ethylacetate. Parameters such as the quantity of catalyst, i.e. Zirconyl chloride and various temperatures were investigated. The reaction mixture was stirred on a magnetic stirrer and progress of the reaction monitored with the help of TLC. The best results were obtained by using optimum amount of catalyst as 250 mg and optimum temperature was found to be 70°C. The optimized conditions were then used for the conversion of various aromatic aldehydes (**1a-1h**) to the corresponding diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridines-3,5-dicarboxylate derivatives (**2a**–**2h** ; Table 2). The results show that the presence of electron-withdrawing and electron-donating substituents on the aromatic ring of the aldehyde has slight influence on the rate of reaction and yield. The rate of reaction and yield of product decreased slightly due to the presence of electron donating group as a result of the decrease in the electrophilicity of the carbonyl carbon, whereas a strong electron-withdrawing group, increased the reaction rate and yield of product slightly. Here various aromatic aldehydes containing electron-donating and electron attracting groups, viz., 4-chlorobenzaldehyde(1a), 2,4-dichlorobenzaldehyde(1b), 4-methylbenzaldehyde (1c), 4-methoxybenzaldehyde (1d), 3,4-dimethoxybenzaldehyde (1e), 4-nitrobenzaldehyde (1f), 3-nitrobenzaldehyde (1g) and 4-bromobenzaldehyde (1h) are used which gave corresponding 1,4-dihydropyridines as products in good yields.

Effect of Catalyst Concentration

The catalyst concentration was varied over a range of 50-300 mg on the basis of the total volume of the reaction mixture. Optimum amount of catalyst was investigated from the reference reaction in which 4-chlorobenzaldehyde, chosen as a representative aldehyde was reacted with ethylacetoacetate and ammonium acetate. The amount of catalyst was varied from 50 mg to 300 mg to observe the effect on the yield of product. Table 1 shows the effect of catalyst concentration on the yield of the corresponding 1,4-DHPs. It has been found that yield of product increased with increasing catalyst concentration from 50 to 250 mg. Further addition of catalyst has however showed a decrease in the yield. Thus, in all other reactions an amount of 250 mg of Zirconyl chloride was used.

Table 1. Catalyst effect on the synthesis of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridines-3,5-dicarboxylate.

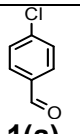
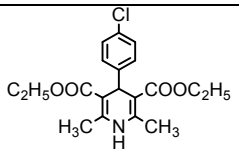
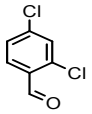
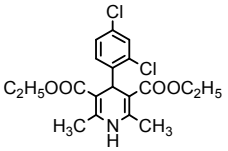
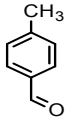
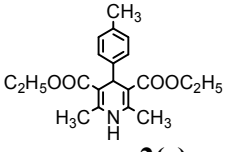
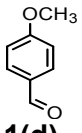
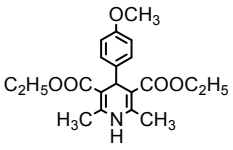
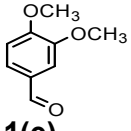
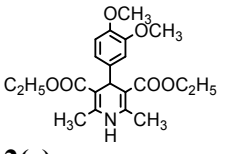
Entry	Amount of Zirconyl chloride (mg)	Reaction time (min.)	Yield (%)
1	50	85	45
2	100	65	55
3	200	45	65

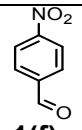
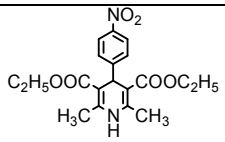
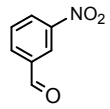
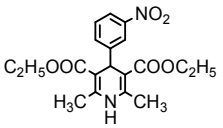
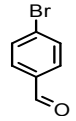
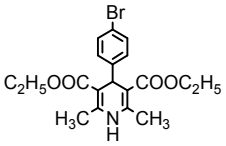
4	250	30	85
5	300	40	75

Synthesis of 1,4-Dihydropyridines catalysed by Zirconyl chloride

The results of the reactions of aryl aldehydes, ethylacetoacetate and ammonium acetate in the presence of Zirconyl chloride at 70ºC are shown in Table 2. Variously substituted aromatic aldehydes bearing either activating or deactivating groups react well with the β-dicarbonyl compound to yield the corresponding 1,4- dihydropyridines. The reactions can be completed in 30-65 min. in good to better yields (60-90%). For larger scale synthesis, a typical reaction (Entry 1 of Table 2) was performed with five times the amounts of reactants and catalyst used in the experimental section, from which a yield of 75 % was obtained.

Table 2. Results of synthesis of 1,4-dihydropyridines in the presence of Zirconyl chloride as per Scheme 1.

Entry	R_1	Product	Time (min)	Yield (%)	m.p (°C) obs/lit.
1	 **1(a)**	 **2(a)**	30	80	142-144°C [lit. 144-146^{0}C] [xii]
2	 **1(b)**	 **2(b)**	45	85	187-189°C [lit. 190-192^{0}C] [xii]
3	 **1(c)**	 **2(c)**	55	60	125-127°C [lit. 128-130^{0}C] [xiii]
4	 **1(d)**	 **2(d)**	50	75	157-159°C [lit. 158-160^{0}C] [xiv]
5	 **1(e)**	 **2(e)**	65	80	130-132°C [lit. 132-134^{0}C] [xv]
6			45	90	132-134°C [lit. 130-132^{0}C]

	 **1(f)**	 **2(f)**			[xiv]
7	 **1(g)**	 **2(g)**	65	75	160-162°C [lit. 162-164^{0}C] [xvi]
8	 **1(h)**	 **2(h)**	50	80	157-159°C [lit. 160-162^{0}C] [xvi]

The physical and spectroscopic data of compounds are as follows:

Diethyl 2,6-dimethyl-4-(4-chlorophenyl)-1,4-dihydropyridines-3,5-dicarboxylate: **2(a)**;
IR (cm^{-1}) : 3421, 3074, 1667; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.07-1.17 (t, J = 7.00 Hz, 6H), 2.36 (s, 6H), 3.56 (q, J = 4.3 Hz, 4H), 4.66 (s, 1H, CH), 5.81 (br, 1H, NH) and 7.07-7.64 (m, 4H, Ar).

Diethyl 2,6-dimethyl-4-(2,4-dichlorophenyl)-1,4-dihydropyridines-3,5-dicarboxylate: **2(b)**;
IR (cm^{-1}) : 3348, 3056, 1669 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09-1.21 (t, J = 7.00, 6H), 2.28 (s, 6H), 3.60 (q, J = 4.3 Hz, 4H), 4.75 (s, 1H, CH), 5.80 (br, 1H, NH) and 7.09-7.58 (m, 3H, Ar).

Diethyl 2,6-dimethyl-4-(4-methylphenyl)-1,4-dihydropyridine-3,5- dicarboxylate: (2c);
IR (cm^{-1}) : 3364, 3091, 1698; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.11-1.26 (t, J = 7.00 Hz, 6H), 2.28 (s, 3H), 2.34 (s, 6H), 4.07 (q, J = 4.3 Hz, 4H), 4.99 (s, 1H, CH), 5.78 (s br, 1H, NH) and 7.06-7.21 (m, 4H, Ar).

Diethyl 2,6-dimethyl-4-(4-methoxyphenyl)-1,4-dihydropyridines-3,5-dicarboxylate: 2(d);
IR (cm^{-1}) : 3409, 3104, 1667; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.19-1.27 (t, J = 7.00 Hz, 6H), 2.17 (s, 6H), 2.78 (s, 3H), 3.98 (q, J = 4.3 Hz, 4H), 5.18 (s,1H, CH), 5.80 (br, 1H, NH) and 7.12-7.30 (m, 4H, Ar).

Diethyl 2,6-dimethyl-4-(3,4-dimethoxyphenyl)-1,4-dihydropyridines-3,5-dicarboxylate: 2(e);
IR (cm^{-1}) : 3373, 3010, 1698; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.15-1.25 (t, J = 7.00 Hz, 6H), 2.19 (s, 6H), 2.88 (s, 3H), 3.01 (s, 3H), 4.12 (q, J = 4.3 Hz, 4H), 5.38 (s, CH), 5.89 (br, 1H, NH) and 7.06-7.20 (m, 3H, Ar).

Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridines-3,5-dicarboxylate: 2(f); IR (cm^{-1}) : 3289, 3040, 1669; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.10-1.21 (t, J = 7.00 Hz, 6H), 2.06 (s, 6H), 4.17 (q, J = 4.3 Hz, 4H), 4.87 (s, 1H, CH), 5.73 (br, 1H, NH) and 7.00-7.23 (m, 4H, Ar).

Diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5- dicarboxylate: (2g); IR (cm^{-1}) : 3346, 2997, 1703; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.14-1.26 (t, J = 7.00 Hz, 6H), 2.40 (s, 6H), 4.09 (q, J = 4.3 Hz, 4H), 4.83 (s, 1H, CH), 5.77 (s br, 1H, NH) and 7.89-8.01 (m, 4H, Ar).

Diethyl 2,6-dimethyl-4-(4-bromophenyl)-1,4-dihydropyridines-3,5-dicarboxylate: 2(h); IR (cm^{-1}) : 3320, 2987, 1668; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.11-1.20 (t, J = 7.00 Hz, 6H), 2.09 (s, 6H), 4.18 (q, J = 4.3 Hz, 4H), 5.01 (s, 1H, CH), 5.66 (br, 1H, NH) and 7.09-7.21 (m, 4H, Ar).

CONCLUSIONS

We have successfully developed an easy, efficient and economical method for synthesis of 1,4-dihydropyridines from the reactions of aryl aldehydes, ethylacetoacetate and ammonium acetate catalysed by Zirconyl chloride. This environmently benign and safe procedure is advantageous in terms of mild experimentation conditions, economic catalyst, good to excellent yield, short reaction times, easy isolation of products, absence of any volatile organic solvent and large scale applicability.

ACKNOWLEDGMENT

The authors are thankful to Head, Department of Chemistry, M. D. University, Rohtak for providing necessary facilities.

REFERENCES

i. Richard, K.; Gonzalez. C. J.; David, J. C. C.; Sarah, R. A.; Inglis, G. G. A.; Fisher, G.; Sherwood, J.; Binks. P. S. and Curzons. A. D.; *Green Chem.* **2011***, 13,* 854.

ii. Shan, R.; Velazquez, C. and Knaus, E. E.; *J. Med. Chem.*, **2004**, 47, 254.

iii. Visentin, S.; Rolando, B.; Stilo, A. D.; Frutterro, R.; Novara, M.; Carbone, E.; Roussel, C.; Vanthuyne, N. and Gasco, A.; *J. Med. Chem.*, **2004**, 47, 2688.

iv. Poindexter, G. S.; Bruce, M. A.; Breitenbucher, J. G.; Higgins, M. A.; Sit, S. Y.; Romine, J. L.; Martin, S. W.; Ward, S. A.; McGovern, R. T.; W. Clarke, W. and Russell J.; *Bioorg. Med. Chem.*, **2004**, *12*, 507.

v. Eharkar, P. S.; Desai, B.; Gaveria, H.; Varu, B.; Loriya, R.; Naliapara, Y.; Shah, A. and Kulkarni, V. M.; *J. Med. Chem.*, **2002**, *45*, 4858.

vi. Klusa, V.; *Drugs Future*, **1995**, 20, 135.

vii. Bretzel, R. G.; Bollen, C. C.; Maeser, E. and Federlin, K. F.; *Am. J. Kidney Dis.*, **1993**, *21*, 53.

viii. Mauzeral, D. and Westheimer, F. H.; *J. Am. Chem. Soc.*, **1955**, *77,* 2261.

ix. G-Choghamarani, A.; Zolfigol, M. A.; Salehi, P.; Ghaemi, E.; Nasr-Isfahanid, E. H. and Shahamirianb, M.; *Acta Chim. Slov.,* **2008***, 55,* 644.

x. Loev, B.; and. Snader, K. M.; *J. Org. Chem.,* **1965**, *30*, 1914.

xi. Sabitha, G.; Arundhathi, K.; Sudhakar, K.; Sastry, B. S. and Yadav, J. S.; *Synth. Commun.* **2009**, *39*, 2843.

xii. Masoud N-E.; Morteza, M. and Razieh R.; *Maejo Int. J. Sci. Technol.* **2014**, *8,* 32.

xiii. Arash, G-C.; Mohammad, A. Z.; Maryam, H.; Hamid G.; Mohsen. N.; Somaieh Y. and Bahman T.; *J. Braz. Chem. Soc.*, **2011**, *22*, 525.

xiv. Debache, A.; Ghalem, W.; Boulcina, R.; Belfaitah, A.; Rhouati, S. and Carboni, B.; *Tetrahedron Lett.,* **2009**, *50*, 5248.

xv. Sivamurugan, V.; Vinu, A.; Palanichamy, M. and Murugesan V.; *Heteroat. Chem.*, **2006**, *17*, 267.

xvi. Mansoor, S. S.; Aswin, K.; Logaiya, K. and Sudhan, S. P. N.; *J. King Saud Univ. Sci.,* **2013**, 25, 191.

Received on June 6, 2016.