One Pot Synthesis of 1, 4 Dihydropyridine Derivatives by IR Irradiation

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Abstract- In the presence of IR irradiation by the use of solid support montmorillonite KSF, under solvent free conditions four component aldehyde, Dione, Meldrum acid and ammonium acetate react for the formation of 1, 4 dihydropyridine derivatives. This is a greener method and one pot synthesis. Minimum reaction time and higher yield are the advantages of this process. The product can be purifying by chromatographic method. The synthesized compounds were also found effective against bacterial and fungal organism. We can use these derivatives for the treatment of disease as an antibacterial and antifungal agent.

Key words- 1,4dihydropyridine, IR irradiation, solvent free synthesis, Multicomponent

I. INTRODUCTION

1,4 dihydropyridine and their derivatives have its great importance in biological activity, like antihypertensive , anti-inflammatory, antihypotoxic, anti-ischemic, calcium channel modulators of the nifedipine , antimicrobial,antianginal, anticancer vulsant neurotropic , glycoprotein inhibitors, bronchodilating, and antidiabetic agents. 1, 4 dihydropyridine has pharmacological and therapeutic significance. For the cure of dangerous tuberculosis disease 3, 5 dicarbamoyl derivative of 1, 4 DHP with lipophilic groups have considerable anti tubercular activity against. Due to these importances the synthesis of 1, 4 DHP derivatives is essential now a days. [1-7]

The green chemistry programme supports the invention of more environment friendly chemical process which reduces or even eliminates the generation of harmful and poisonous substance. [8 -10]

On the other hand multicomponent reactions have drawn great interest enjoying an outstanding status in modern organic synthesis and medicinal chemistry because they are one – pot processes bringing three or more component and show high atom economy. Multicomponent reaction play an important role in the synthesis of complex & important organic molecules (which are useful in the discovery of drugs) from simple & readily available starting materials. [11 – 20]

Due to simple experimental technique solvent free reactions reduce pollution and bring down handling cost. If two, three or many substances are involved in the reaction, they are ground together in a glass mortar or co-crystallized and allowed to stay at room temperature or transferred to a suitable apparatus and heated carefully in an oil bath or exposed to appropriate radiation until the reaction is complete.

The traditional heating equipment like oil bath & heating jacket often generate a temperature gradient with local over heating of the sample which can undergo decomposition.IR irradiation is characterized by uniform heating throughout the material which allow high efficiency & improved reproductivity of the chemical process

In this context the combination of IR irradiation & solvent free condition in organic synthesis provide clean chemical process characterized by enhanced reaction rate & higher yield. [21 – 30]

Here in we would like to report an efficient procedure for the preparation of 1, 4 dihydro pyridine derivatives through a four component reaction including 1, 3 Dione (1), aldehyde (2), Meldrum acid (3) and ammonium acetate (4) in the IR irradiation.

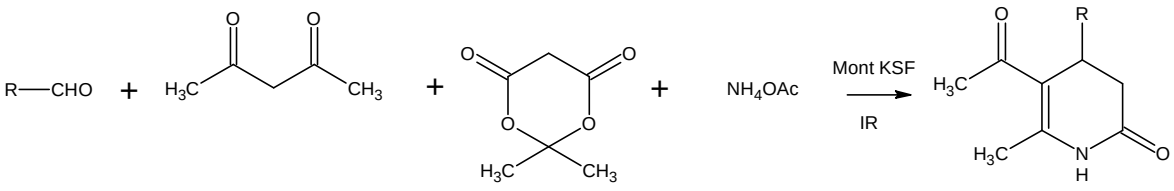
II. RESULT AND DISCUSSING ON

We want to develop such method for the preparation of biologically compounds, which are novel yet resemble known biologically active molecules by virtue of the presence of some critical structural features, we have developed a facile, efficient, one-pot method for the synthesis of novel 1, 4 dihydro pyridine derivatives.

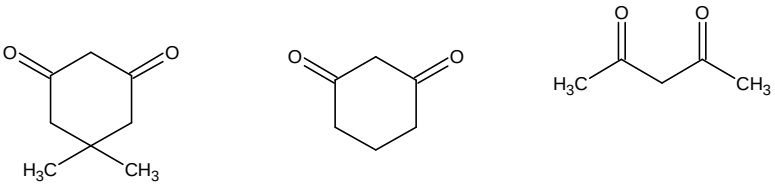
The required biologically important 1, 4 dihydro pyridine derivatives were prepared by the improved solvent free multi component reaction b/w p-nitrobenzaldehyde (1a), 5, 5-dimethyl-1,3cyclohexanedione (2a), Meldrum acid (3) & ammonium acetate (4) using montmorillonite (KSF) as solid support, under IR irradiation.

The classical method involving either the azeotropic removal of water or reaction in presence of dehydrating agent and use of large amount of volatile and toxic solvents at elevated temperature for several hours of heating was of some utility. The yield of the product was carried out conventionally.

The montmorillonite KSF was found to be the best solid support giving the maximum (88%) yield of the required product reasonable purity (TLC) with shortest reaction time & easier work-up.



1 2 3 4 5



2(a) 2(b) 2(c)

Table-1

Entry	Products	R	2	Reaction time (min.)	Isolated yield (%)	Mp. (°c)
1	5a	C_6H_5	2a	5-10	90%	211-213
2	5b	p-ClC_6H_4	2a	5-10	86%	188-190
3	5c	p-$CH_3C_6H_4$	2a	5-10	86%	199-201
4	5d	p-$NO_2C_6H_4$	2b	5-10	87%	222-224
5	5e	p-ClC_6H_4	2b	5-10	82%	177-179
6	5f	m-$NO_2C_6H_4$	2c	5-10	45%	175-178

Table-2

Synthesis of 1, 4 dihydropyridine derivatives-

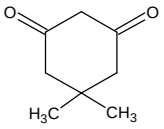
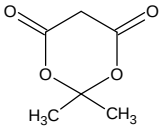
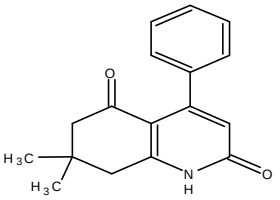
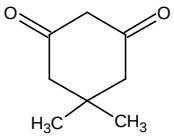
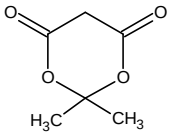
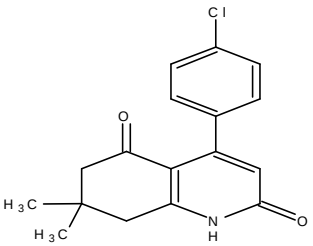
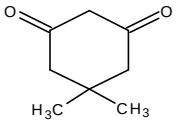
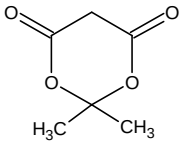
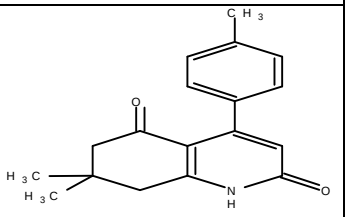
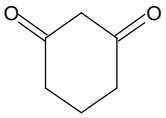
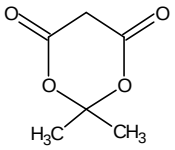
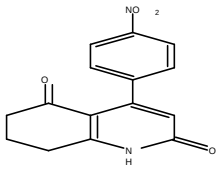
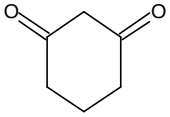
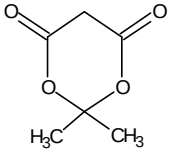
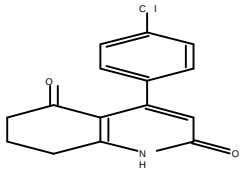
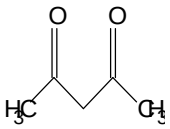
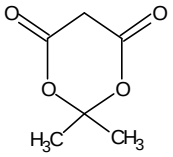
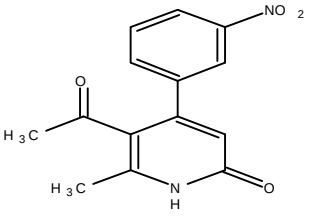
Entry	Reactant				Product
	(1)	(2)	(3)	(4)	
1	C_6H_5CH0			NH_4OAc	
2	p-ClC_6H_4CHO			NH_4OAc	
3	p-$CH_3C_6H_4CHO$			NH_4OAc	
4	p-$NO_2C_6H_4CHO$			NH_4OAc	
5	p-ClC_6H_4CHO			NH_4OAc	
6	m-$NO_2C_6H_4CHO$			NH_4OAc	

Table- 3

Antibacterial activity of compounds (newly synthesized 1, 4 dihydropyridine derivatives (5a-5f)) against Staphylococcus aureus (disk diameter 7 c.m.)-

Compound	Concentration of compounds %	IZ of sample c.m.	IZ of a standard ciprofloxacin, c.m.	AI
5(a)	100	6	21	0.29
5(b)	100	16	21	0.76
5(c)	100	22	21	1.048
5(d)	100	12	21	0.57
5(e)	100	12	21	0.57
5(f)	100	10	21	0.48

Table-4

Antibacterial activity of compounds (newly synthesized 1, 4 dihydropyridine derivatives (5a-5f)) against Bacillus subtillus-

Compound	Concentration of compounds %	IZ of sample c.m.	IZ of a standard ciprofloxacin, c.m.	AI
5a	100	6	18	0.33
5b	100	15	18	0.83
5c	100	12	18	0.67
5d	100	13	18	0.72
5e	100	11	18	0.61
5f	100	15	18	0.83

Table-5

Antifungal activity of compounds (the newly synthesized 1, 4 dihydropyridine derivatives (5a-5f)) against A.Parasitica-

Compound	Concentration of compounds %	IZ of sample c.m.	IZ of a standard clotrimazole, c.m.	AI
5a	100	8	24	0.33
5b	100	6	24	0.25
5c	100	14	24	0.58
5d	100	16	24	0.67
5e	100	14	24	0.58
5f	100	15	24	0.63

Table-6

Antifungal activity of compounds (the newly synthesized 1, 4 dihydropyridine derivatives (5a-5f)) against Chrysosporium sp:-

Compound	Concentration of compounds %	IZ of sample c.m.	IZ of a standard clohimazole c.m.	AI
5a	100	7	22	0.32
5b	100	15	22	0.23
5c	100	12	22	0.55
5d	100	13	22	0.59
5e	100	12	22	0.55
5f	100	21	22	0.95

Table-7

Antibacterial activity of mixture of compounds (the newly synthesized 1, 4 dihydropyridine derivatives (5a-5f)) against Staphylococcus aureus and Bacillus subtillus-

Compound	Test strain	Concentration of compounds, %	IZ of sample c.m.	IZ of a standard ciprofloxacin	AI
Mixture of compound	S.aureus	100	22	21	1.048
Mixture of compound	B.subtillus	100	15	18	0.83

Table-8

Antifungal activity of mixture of compounds (the newly synthesized 1,4 dihydropyridine derivatives (5a-5f)) against A.Parasitica and Chrysosporium sp:-

Compound	Test strain	Concentration of compounds, %	IZ of sample c.m.	IZ of a standard clohimazole	AI
Mixture of compound	A.Parasitica	100	16	24	0.67
Mixture of compound	Chrysosporium sp.	100	21	22	0.95

The structure assigned for the reaction product is established from analytical data.

Antifungal and antibacterial activity of the newly synthesized 1, 4 dihydropyridine derivatives (5a-5f) was screened using disc diffusion method. The results are presented in table 3 to 8. The newly synthesized compounds show antibacterial and antifungal activity alone and in combinations.

A. Antibacterial activity

The diameter of the inhibitions zones obtained upon treatment with compounds and mixture of compounds at concentration of 100% was 6, 16, 22, 12, 12, 10 c.m. against Staphylococcus aureus and 6, 15, 12, 13, 11, 15 against Bacillus subtillus. Standard reference drug Ciprofloxacin showed inhibition zone of 21 and 18 c.m. against S. Aureus and B. Subtillus.

Inhibition zone of the mixture of compounds were found to be higher than those of single compounds and reference antibiotics. The presence of nitro group in compounds plays an important role in antibacterial activity. The nitro group present on the phenyl ring generally followed by bacterial cell death.

B. Antifungal activity

The diameter of the inhibition zones obtained upon treatment with compounds and mixture of compounds at concentration of 100% was 8, 6, 14, 16, 14, 15 c.m. against A.Parasitica and 7, 5, 12, 13, 12, 21 c.m. against Chrysosporium sp.

Standard reference drug clotrimazole showed inhibition zone of 24 and 22 c.m. against A.Parasitica and Chrysosporium sp. Presence of sulphur and nitrogen, presence of methyl group along with nitro on phenyl ring indicate higher efficiency against fungal strains. We conclude the mixture of compounds and single compound can be used as antibacterial and antifungal agent.

III. EXPERIMENTAL METHOD

In open capillaries melting point can be taken. By TLC (thin layer chromatography) method we can measure the purity of compounds on precoated silica gel aluminum plates & visualized by exposure to ultraviolet light (254nm) or iodine vapors. The IR spectra of the compound were recorded on FT-IR spectro photometer; H-NMR spectra of selected compound were recorded on multinuclear.

IV. EXPERIMENT

1, 4 DHPS derivatives 5a were synthesized by following method:-

A. Conventional Method-

m- nitrobenzaldehyde (1a, 0.6m mol), 1, 3-cyclohexadione (1a, 0.6m mol), meldrum acid (3, 0.6m mol) & ammonium acetate (4, 0.9m mol) were taken in required quantity & refluxed for 5-6 h.

In cold water the precipitate of synthesized compound was pured & by the use of glacial acetic acid precipitate can be acidified. After it we filter the precipitate, dry and then crystallized by the use of ethanol, to give the desired product 5a in an excellent yield.

B. Non-conventional method-

using inorganic solid support:- a mixture of 0.6m mol (1a) , 0.6m mol (2a), 0.6m mol (3) & 0.9m mol (4) were absorbed on montmorillonite KSF (6g) with methanol, mixed thoroughly and irradiated by IR irradiation for an appropriate time until the completion of the reaction (monitored by TLC).

Recyclable solid support was separated by filtration after eluting the product with methanol and excess solvent was evaporated on a rotary evaporator to give solid. For spectral studies and elemental analyses, compound (5a-5f) was further recrystallized from methanol.

(5a) yield 90%, mp. 211-213^{0}c, reaction time- 5-10 min., Anal. Found: C, 76.36; H, 6.41; N, 5.242, Calc. $C_{17}H_{17}NO_2$: C, 76.50; H, 6.37; N, 5.27. IR (KBr) max 3078(aromatic-H), 1690(C=O), 1590(C=C), ^{1}HNMR ($CDCl_3$) (ppm); 6.89-7.58(10H, Ar-H), 2.31(S, 6H, $(CH3)_2$), 8.02(S, 1H, NH)
(5b) yield 86%, mp. 188-190^{0}c, reaction time 5-10 min., Anal. Found: C, 67.77; H, 5.32; Cl, 11.627; N, 5.172, Calc. $C_{17}H_{16}ClNO_2$: C, 67.90; H, 5.28; N, 3.20. IR (KBr) max 3084 (aromatic C-H), 1698(C=O), 1580(C=C), ^{1}HNMR ($CDCl_3$) (ppm) 6.69-7.59 (m, 9H, ArH), 7.98(S, 1H, NH), 2.21(S, 6H, $(CH3)_2$)

(5C) yield 86%, mp. 199-201^{0}c, reaction time – 5-10 min. Anal. Found: C, 76.55; H, 7.14; N, 4.96, Calc. $C_{18}H_{20}NO_2$: C, 76.70; H, 7.12; N, 4.98. IR (KBr) max 3080 (aromatic C-H), 1694 (C=O), 1595 (C=C), ^{1}HNMR ($CDCl_3$) (ppm) 6.59-7.78 (m, 9H, ArH), 2.38 (S, 6H, $(CH3)_2$), 7.58 (S, 1H, NH)

(5D) yield 87%, mp. 222-224^{0}c, reaction time 5-10 min, Anal. Found: C, 65.31; H, 4.42; N, 5.12, Calc. $C_{15}H_{12}ClNO_2$: C, 65.47; H, 4.38; N, 5.13. IR (KBr) max3079 (aromatic C-H), 1670 (C =O), 1590(C=C), ^{1}HNMR ($CDCl_3$), (ppm); 7.70-7.85 (m, 11H, ArH), 7.69 (S, 1H, NH)

(5e) yield 82%, mp. 177-1790c, reaction time 5-10 min., Anal. Found: C, 61.74; H, 4.44; N, 10.29, Calc. $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.39; N, 10.31. IR (KBr) max 3075(aromatic C-H), 1695(C=O), 1584(C=C), ^{1}HNMR ($CDCl_3$), (ppm), 6.72-7.60 (m, 11H, ArH), 7.59(S, 1H, NH)

(5f) yield 45%, mp. 175-1780c, reaction time 5-10 min., Anal. Found: C, 63.36; H, 4.25; N, 9.85, Calc. $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.23; N, 9.90. IR (KBr) max 3090(aromatic C-H), 1689(C=O), 1590(C=C), ^{1}HNMR ($CDCl_3$), (ppm), 6.69-7.13 (m, 5H, ArH), 7.92 (S, 1H, NH), 2.25 (S, 6H, $(CH3)_2$)

V. BIOLOGICAL ACTIVITY

A. Antibacterial activity

The effect of various plant extracts on the several bacterial strains was essayed by Agar well diffusion method. Precipitate containing 20ml. Muller Hinton medium was seeded with 24hr. in bacterial strain's culture. Wells were cut and 20ul of the plant extracts (namely aqueous, method and chloroform extracts) were added.

The plates were then incubated at 370c for 24hr. The antibacterial activity was assayed by measuring the diameter of the inhibition zone formed around the well. Ciprofloxacin disc was used as a positive control.

B. Antifungal activity

The activity of the plant extracts on various fungal strains was assayed by Agar plug method. The fungicidal effect of the plant extracts can be assessed by the inhibition of mycelia

Growth of the fungus and is observed as a zone of inhibition near the disc or the wells.

Potato Dextrose Agar medium was prepared and poured on the precipitates. A fungal plug was placed in the center of the plates. Sterile discs immersed in the plates extracts were also placed in the plates .clotrimazole was used as antifungal controller. The effect of antifungal activity was seen as crescent shaped zone of inhibition

VI. CONCLUSION

An efficient, clean, green methodology and environmental friendly procedure for preparation of hydrogenated pyridine derivatives has been described in this paper. Montmorillonite KSF mediated one pot synthesis of 1,4 dihydropyridine derivatives has the advantages of mild conditions , good yield, high versatility, non toxic reaction medium and ease of recovery and reuse of the reaction medium. All these merits make the method attractive for scale-up preparation of DPP_S derivative

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REFERENCES

[1] K.J.Chleifer; J. Med. Chem.; 1999; 42; 2204
[2] S.Visentin,P.Amiel,R.Frittero,D.Boschi,C.Roussel,L.Giusta,E.Carbone,Gasco; J.Med.Chem.; 1999; 42 ; 1422
[3] B.Schnell, W.Krenn, K.Faber, C.O.Kappe; J. Chem. Soc. Perkin Trans 1; 2000; 24; 4382
[4] T.Lavanya,S.Manjula,Raj Kiran Ellandala, T. Pradeep Kumar and K.Madhavi; I.J.R.P.C; 2011, 1, 4
[5] X. Zhou, L. Zhang , E. Tseng , E. Scott Ramsay, J. J. Schentag , R.A.Coburn , M.E. Morris; Drug Metabolism and Disposition ; 2005 ; 33 ; 321-328.
[6] A.R. Trivedi, D.K. Dodiya , B.H. Dholariya, U.B. Katariya, V.R. Bhuva , V.H.Shah; Bioorganic &Medicinal Chemistry Letters ; 2011 ; 21 ; 5181-5183
[7] M.Khoshneviszadeh , N. Edraki , K. Javidnia , A. Alborzi , B. Pourabbar , J. Mardaneh, R. Mir; Bioorganic & Medicinal Chemistry ; 2009 ; 17 ;1579- 1586
[8] Clark J.H., Loque R. , Matharu A.S. ; "Green, biofuels and biorefinery" ; Annual review of chemical and bimolecular engineering ; 2012 ;3; 183-207.
[9] Kira J.M. Maths, Julie B Zimmerman and Evan Beach; "A Proactive approach to toxic chemicals, moving green chemistry beyond alternatives in the "safe chemicals" act of 2010"; Environ. Sci. Tech.; 2010; 44; 6022-6023.
[10] Sweta Sharma, Saloni gangal and A.Rauf; "Green chemistry approach to the sustainable advantages to the synthesis of heterocyclic chemistry" Rasayan J. Chem.; 2008; 1; 693-712.
[11] Alezandas domlity; "The discovery of new isocyanides based multicomponent reactions." Current opinion in chemical biology; 2004;. 4; 318-323
[12] James E. Biggs- Houck, A. Younai, Jared and Shaw; "Recent advances in multicomponent reaction for diversity- oriented synthesis"; current opinion in chemical biology; 2010; 14; 371-382.
[13] N. Azizi, F.Ebrahimi and M.R. Saeidi; "Highly efficient under solvent free conditions"; scintia, Iranica, Iransachain C; 2009; 16; 94-98.
[14] Orru, R.V.A, Ruijler, E. (Eds.) Synthesis of heterocycles via multicomponent reaction; Springer; Heidelberg, 2010; 1-2.
[15] Toure, B.B.; Hall, Chem. Rev. 2009; 109; 4439.

[16] D' Souza D.M. and Muells T.J.J.; Chem. Soc. Rev.; 2007; 36; 1095.
[17] Kalinski C., Lemoine H., Schmidt J., Burdack c, Kolb J., Umkehres M. And Ross G.; Synlett. 2008; 24; 4007.
[18] Toure, B.B., Hall, D.G. Natural product synthesis using multicomponent reaction strategies. Chem. Rev.; 2009; 109; 4439-4486.
[19] Bendock S., Fadaly, W.Metwally, M.A. Recent trends in the chemistry of 2-aminobenzothiazoles. J.; Sulfur Chem.; 2009; 30; 74-107.
[20] Ganem B.,Strategies for innovation in multicomponent reaction design, ACC.Chem. Res.' 2009; 42; 463-472.
[21] A.N.M.M. Rahman, R. Bishop, R. Tan and N. Shan; "Green reaction under solvent free condition" ; Green Chem.; 2005; 7; 207.
[22] B. Perio, M.J. Dozias, P. Jacquault and J. Hamelin; "solvent free organic synthesis"; Tetrahedron Lett.; 1997; 38; 7867.
[23] B.C. Ranu, A. Hajra and S.S. Dey; "Greens reaction under solvent free condition"; Organic Process Research and development; 2002; 6; 817.
[24] D. Rajagopal, R. Narayanan and S. Swaminathan; " Organic synthesis under solvent free conditions"; Proc. Indian Acad. Sci. (Chem. Sci.); 2001; 113; 197-213.
[25] G. Najendrappa; "Organic synthesis under solvent free conditions"; Resonance; 2000; 7; 1025-1074.
[26] G. Rothenberg, A.P. Downie, C.L. Raston and J.L. Scott; " Understating solid – solid organic Reaction"; J. Amer. Chem. Soc.; 2001; 123; 8701-8708.
[27] G. Najendrappa; "Organic synthesis under solvent free conditions"; Resonance; 2002; 7; 64-77.
[28] Hiren M. Marvaniya, kaumil N. Modi and Dhrubo Jyoti Sen.; " Green reactions under solvent free conditions"; Int. J. Drug Dev. & Res. ; 2011; 3; 33-34.
[29] M. Kidroai; " Greens reactions under solvent free conditions"; Pure Appl. Chem.; 2001; 73; 147.
[30] Nasir Baig RB, Varma RS, Alternative energy input: Mechano chemical, microwave and ultra sound assisted organic synthesis, Chem. Soc. Rev.; 2012; 41; 1559-1584