SYNTHESIS, EXPERIMENTAL AND DFT STUDIES ON THE CRYSTAL STRUCTURE, FTIR, ¹H NMR AND ¹³C NMR SPECTRA OF DRIVATIVES OF DIHYDROPYRIDINES

LEILA ZARE FEKRI^a, MOHAMMAD NIKPASSAND^{*b}

^aDepartment of Chemistry, Payame Noor University, PO Box 19395-3697 Tehran, Iran

^bDepartment of Chemistry, Rasht Branch, Islamic Azad University, Rasht, Iran

(Received: November 30, 2011 - Accepted: August 6, 2012)

ABSTRACT

Several derivatives of dihydropyridines are prepared through the condensation of aldehydes, dimedone and NH₄OAc in H₂O, in the presence of a catalytic amount of nano-Fe₃O₄. The crystalline products were characterized by FTIR, ¹H NMR and ¹³C NMR. Density Functional Theory (DFT) calculations at the B3LYP level is used to optimize the geometries of isolated molecules, and to calculate the, FTIR, ¹H NMR and ¹³C NMR spectra of selected synthesized compounds. We found that the DFT B3LYP calculated FTIR, ¹H NMR and ¹³C NMR spectra are in accordance with the experimental data.

Keywords: dihydropyridines, nano-Fe₃O₄, FTIR, DFT, B3LYP, NMR.

INTRODUCTION

1, 4- dihydropyridines (1, 4- DHPs) and their derivatives are an important class of bioactive molecules in the field of drugs and pharmaceutical ¹. The heterocyclic ring in DHP is a common feature of various bioactive compounds such as anticonvulsant, antidiabetic, antianxiety, antidepressive, antitumor, analgesic, sedative, vasodilator, bronchodilator, hypnotic and anti-inflammatory agents ². DHPs are commercially used as calcium channel blockers for the treatment of cardiovascular diseases including hypertension ³.

Starting from Hantzsch more than a century ago, there are several efficient methods developed for the synthesis of 1, 4-dihydropyridines ⁴, which comprise the use of microwave ⁵, ionic liquid ⁶, high temperature in refluxing solvent ⁷, TMSCl-NaI ⁸, metal triflates ⁹, I₂ ¹⁰ and CAN ¹¹. However, these methods suffers several disadvantages such as long reaction times, excess of organic solvent, lower product yield, harsh refluxing condition, use of high temperatures, extensive amounts of reagents, occurrence of several side products and difficulty in the recovery and reusability of the catalyst. Thus, the development of a simple, efficient and versatile method for the preparation of dihydropyridines is an active area of research and there is a scope for further improvement towards milder reaction condition and higher product yields.

In recent years, density functional theory (DFT) calculations have been used extensively for calculating a wide variety of molecular properties such as equilibrium structure, charge distribution, FTIR and NMR spectra, and provide reliable results which are in agreement with experimental data ¹². In this research, Beck's three-parameter exchange functional ¹³ with Lee, Yang and Parr's ¹⁴ correlation functional (B3LYP), developed by Truhlar et al., ¹⁵ are used to perform theoretical calculations on the structure, FTIR, ¹H NMR and ¹³C NMR spectra and some additional properties of the title compounds.

EXPERIMENTAL

Materials and measurements

IR spectra were determined on a Shimadzu IR-470 spectrometer. ¹H NMR spectra were obtained on a Bruker DRX 500, and 250 and ¹³C NMR spectra on a Bruker DRX 125 Avance spectrometer, in CDCl₃ as solvent and with TMS as internal standard. Chemicals were purchased from Merck and Fluka. Elemental analyses were done on a Carlo-Erba EA1110CNNO-S analyzer and agreed with the calculated values. All used solvents were dried and distilled according to standard procedures.

Preparation of dihydropyridines 3a-3j

A mixture of aldehyde (1 mmol), dimedone (2 mmol), NH₄OAc (1mmol) and 0.05 g nano-Fe₃O₄ in 10 mL H₂O were refluxed for the required reaction times (8-15 minutes). The progress of the reaction was monitored by TLC (EtOAc:petroleum ether 1:4). After completion of the reaction, the mixture was filtered in the presence of an efficient magnetic bar to separate it from the catalyst. The product was recrystallized from ethanol to produce 1, 4-dihydropyridine derivatives 3a-j as pure crystalline products.

3,3,6,6-tetramethyl-9-(2-nitrophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3b)

Yellow-orange solid, mp 282-283 °C. IR (KBr): ν 3450, 3080, 2980, 1650, 1540, 1520, 1480, 1360, 1345, 1220 Cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 0.96 (s, 6H), 1.06 (s, 6H), 2.23-2.46 (m, 8H), 5.80 (s, 1H), 7.21 (t, J = 6.99 Hz, 1H), 7.39-7.35 (d, J = 6.81Hz, 1H), 7.41-7.48 (m, 2H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 27.8, 29.5, 32.9, 41.2, 51.1, 112.9, 124.5, 127.0, 132.5, 134.2, 141.2, 149.6, 149.8, 195.9 ppm. Anal. Calcd. for C₂₃H₂₆N₂O₄: C, 70.03; H, 6.63; N, 7.10. Found: C, 70.25; H, 6.48; N, 7.02.

3,3,6,6-tetramethyl-9-(3-nitrophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3c)

Off white solid, mp 273-275 °C. IR (KBr): ν 3380, 3060, 1645, 1610, 1480, 1520, 1360, 1340 Cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 0.86 (s, 6H), 1.01 (s, 6H), 2.0 (d, J = 16.3Hz, 2H), 2.10 (d, J = 16.3Hz, 2H), 2.28 (d, J = 17.1Hz, 2H), 2.35 (d, J = 17.1Hz, 2H), 5.01 (s, 1H), 7.29 (t, J = 7.86 Hz, 1H), 7.65 (d, J = 6.9Hz, 1H), 7.83 (d, J = 8.1Hz, 1H), 8.02 (s, 1H), 8.90 (s, br, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 27.4, 30.0, 33.0, 34.5, 51.1, 112.2, 121.2, 123.1, 130.0, 135.2, 148.4, 149.6, 150.2, 195.6 ppm. Anal. Calcd. for C₂₃H₂₆N₂O₄: C, 70.03; H, 6.63; N, 7.10. Found: C, 69.88; H, 6.52; N, 7.28.

3,3,6,6-tetramethyl-9-(4-nitrophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3d)

Yellow-orange solid, mp 282-283 °C. IR (KBr): ν 3384, 3070, 2956, 1643, 1540, 1460, 1360, 1342, 1130, 840 Cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 0.87 (s, 6H), 1.02 (s, 6H), 2.04 (d, J = 16.3 Hz, 2H), 2.15 (d, J = 16.3 Hz, 2H), 2.26 (d, J = 17.0 Hz, 2H), 2.34 (d, J = 17.0 Hz, 2H), 5.05 (s, 1H), 7.44 (t, J = 8.5 Hz, 2H), 7.98 (d, J = 6.9 Hz, 2H), 8.49 (s, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 27.4, 29.9, 32.9, 34.9, 51.0, 109.2, 112.3, 123.5, 129.3, 146.3, 149.8, 154.9, 195.6 ppm. Anal. Calcd. for C₂₃H₂₆N₂O₄: C, 70.03; H, 6.63; N, 7.10. Found: C, 69.93; H, 6.75; N, 7.32.

9-(2-chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3e): Off white solid, mp 217-219 °C, IR (KBr): ν 3400, 2980, 1660, 1620, 1465, 1350, 1200 Cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 1.05 (s, 6H), 1.14 (s, 6H), 2.10-2.30 (m, 4H), 2.45-2.62 (m, 4H), 5.04 (s, 1H), 7.09 (d, J = 7.2 Hz, 1H), 7.01-7.19 (m, 1H), 7.25 (d, J = 7.5 Hz, 1H), 7.47 (d, J = 6.4 Hz, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 27.8, 29.7, 32.5, 41.2, 51.2, 114.2, 126.8, 127.6, 129.5, 128.2, 130.6, 130.2, 133.9, 163.5, 197.0 ppm. Anal. Calcd. for C₂₃H₂₆ClNO₂: C, 71.96; H, 6.82; N, 3.65. Found: C, 71.72; H, 6.55; N, 3.81.

9-(4-chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3f): Yellow solid, mp 228-229 °C. IR (KBr): 3440, 3178, 3020, 2958, 1641, 1606, 1488, 1020, 850 Cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 1.03 (s, 6H), 1.15 (s, 6H), 2.17-2.33 (m, 8H), 5.51 (s, 1H), 7.20 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 8.06 (s, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 27.5, 30.0, 33.0, 41.1, 51.2, 113.3, 128.5, 129.9, 132.0, 145.6, 149.7, 196.4 ppm. Anal. Calcd. for C₂₃H₂₆ClNO₂: C, 71.96; H, 6.82; N, 3.65. Found: C, 71.83; H, 6.71; N, 3.55.

9-(3-bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3g): Off white solid, mp 305-307 °C, IR (KBr): ν 3280, 3080, 2970, 1640, 1555, 1250, 1220 Cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 1.01 (s, 6H), 1.12 (s, 6H), 2.18-2.35 (m, 8H), 5.05 (s, 1H), 7.11 (t, J = 7.74 Hz, 1H), 7.35 (t, J = 7.59 Hz, 1H), 7.48 (s, 1H), 7.98 (s, 1H)

ppm. ^{13}C NMR (125 MHz, CDCl_3): δ = 27.5, 30.0, 33.1, 41.1, 51.3, 113.1, 122.6, 127.5, 129.5, 130.0, 131.4, 149.3, 149.8, 196.3 ppm. Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{BrNO}_2$: C, 64.49; H, 6.11; N, 3.27. Found: C, 64.66; H, 6.32; N, 3.11.

9-(4-fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3h): Yellow solid, mp 215-218 °C. IR (KBr): 3355, 3047, 2958, 1653, 1618, 1498, 1147, 891 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ = 0.98 (s, 6H), 1.10 (s, 6H), 2.04-2.38 (m, 8H), 5.09 (s, 1H), 6.90 (m, 2H), 7.30 (m, 2H), 8.30 (s, 1H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ = 27.4, 30.0, 33.0, 41.0, 51.3, 107.2, 113.3, 115.0 (d, $^3J_{\text{CF}}$ = 83.5 Hz), 129.7 (d, $^3J_{\text{CF}}$ = 31.0 Hz), 143.0, 149.9, 162.5 (d, $^1J_{\text{CF}}$ = 249.0 Hz), 196.5 ppm. Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{FNO}_2$: C, 75.18; H, 7.12; N, 3.81. Found: C, 75.32; H, 7.23; N, 3.67. The detailed descriptions of FTIR and NMR spectra of the selected synthesized compounds are given in the next sections.

RESULTS AND DISCUSSION

Recent development in the dihydropyridines chemistry and our continued interest in the development of an efficient and environmentally friendly procedure for the synthesis of pharmaceutical compounds [16-18] triggered us to synthesize derivatives of dihydropyridines and calculate the FT-IR, ^1H NMR and ^{13}C NMR spectra of selected compounds at the B3LYP level. Nano- Fe_3O_4 was initially prepared (Figure 1) and used as a green catalyst for the synthesis of dihydropyridines, as shown in (Scheme 1).

Figure 1. SEM image of synthesized nano- Fe_3O_4

Scheme 1. Schematic representation of the synthesis of DHPs

With the best catalyst in hand, we moved to study the effects of catalyst amount on the model reaction and the results were listed in Table 1. 0.05g of nano- Fe_3O_4 is sufficient to push the reaction forward completion. Higher amount of catalyst did not lead to significant change in the reaction yields.

Table 1. The effect of amount of nano- Fe_3O_4 for the synthesis of 3a.

entry	catalyst	Catalyst amount(%)	Time(min)	Yield(%) ^a
1	-	-	720	No reaction
2	Fe_3O_4	50mg	50	76
3	Nano- Fe_3O_4	50mg	10	96
4	Nano- Fe_3O_4	10mg	30	83
5	Nano- Fe_3O_4	30mg	20	92

a. isolated yield.

With the best quantity of nano- Fe_3O_4 in hand, we were interested to synthesis several dihydropyridines in the multicomponent reaction of various aldehydes, dimedone and NH_4OAc with this catalyst. The results are summarized in Table 2.

Table 2. Synthesis of fused 1, 4-dihydropyridine derivatives (3a-j) using nano- Fe_3O_4 .

Entry	aldehydes	In the presence of Nano- Fe_3O_4		Mp(°C)
		Time (min)	Yield (%) ^a	
a	$\text{C}_6\text{H}_4\text{CHO}$	10	96	189-200
b	2- NO_2 $\text{C}_6\text{H}_4\text{CHO}$	14	91	282-283
c	3- NO_2 $\text{C}_6\text{H}_4\text{CHO}$	12	95	273-275
d	4- NO_2 $\text{C}_6\text{H}_4\text{CHO}$	8	98	282-283
e	2- $\text{ClC}_6\text{H}_4\text{CHO}$	15	94	217-219
f	4- $\text{ClC}_6\text{H}_4\text{CHO}$	11	95	228-229
g	3- $\text{BrC}_6\text{H}_4\text{CHO}$	13	90	305-307
h	4- $\text{FC}_6\text{H}_4\text{CHO}$	8	88	215-218
i	4- $\text{CH}_3\text{OC}_6\text{H}_4\text{CHO}$	15	84	211-212
j	4- $\text{HOC}_6\text{H}_4\text{CHO}$	15	86	274-275

^a isolated yield

Apart from the mild condition of the process and its excellent results, the simplicity of product isolation, replacement of carcinogenic solvent by H_2O and the possibility to recycle nano- Fe_3O_4 offer a significant advantage. After the reaction was completed, the catalyst could be easily attracted by an efficient magnetic bar. After further treatments including washing with CHCl_3 and activation at 80°C, the recycled catalyst has been examined in following runs. Studies on the synthesis of 3a as model substrate showed that the recovered catalyst could be successively recycled in subsequent reactions without any decrease of yields (Figure 2).

Figure 2. Reusability of nano- Fe_3O_4 in the synthesis of 3a.

In the continuation of our study, we concentrated on the calculation of the FT-IR, ^1H NMR and ^{13}C NMR spectra of these compounds at the B3LYP level. The geometries were optimized at the B3LYP level of theory along with standard 6-31G(d) basis set as shown in Figure 3. The harmonic vibrational frequencies were calculated by this method and the results were compared with experimental FTIR spectrum. The most widely used technique for calculating NMR shielding tensors is the GIAO (Gauge Including Atomic Orbital) method. This method was used for calculating ^1H NMR and ^{13}C NMR chemical shifts at the B3LYP/6-31G(d) level. All the calculations were carried out with the Gaussian03 software ¹⁹.

Figure 3. The geometry optimization of 3d, 3f and 3h.

The structure and the scheme of numbering the atoms of 3d, 3f and 3h are shown in Figure 4.

Figure 4. Structure and atom numbering scheme of 3d, 3f and 3h.

The optimized structural parameters bond length and bond angle for the thermodynamically preferred geometry (Figure 3) of 3d, 3f and 3h determined at B3LYP/6-31G level are presented in Table 3 in accordance with the atom numbering scheme of the molecule shown in Figure 4. From the structural data, it is observed that the various C–C bond distances calculated between the carbon atoms and the C–H and C–N bond length are found to be nearly the same in 3d, 3f and 3h structures. The influence of the substituent on the molecular parameters, particularly in the C–C bond distance of ring carbon atoms seems to be negligibly small. The calculated bond angles are very close to each other in these molecules. Investigation of bond angles between N₁–C₂–C₃ and N₁–C₈–C₁₃ shows that these atoms were hybridized sp² and they are completely planar. This experimental data is indicative clearly that there is a pronounced mesomeric interaction between NH and C=O group that is shown in Scheme 2.

Scheme 2. Schematic mesomeric interaction in 3d

Table 3. The selected structural parameters calculated for 3d, 3f and 3h by DFT/B3LYP method with a 6-31G basis sets.

parameters	3d	3f	3h		3d	3f	3h
Bond length(A)				Bond angles(°)			
N ₁ -C ₂	1.3853	1.3966	1.3872	N ₁ -C ₂ -C ₃	120.04	120.68	119.94
N ₁ -H ₃₀	1.0106	0.9934	1.01058	N ₁ -C ₈ -C ₁₃	119.99	120.66	119.94
C ₂ -C ₃	1.3590	1.3672	1.3585	C ₂ -N ₁ -H ₃₀	118.46	118.52	118.32
C ₃ -C ₁₄	1.5221	1.5021	1.5210	C ₂ -N ₁ -C ₈	122.04	119.23	121.91
C ₃ -C ₄	1.4685	1.4670	1.4689	C ₂ -C ₃ -C ₄	120.04	121.28	119.89
C ₁₄ -C ₁₅	1.5327	1.5059	1.5340	C ₃ -C ₁₄ -C ₁₃	110.14	110.81	109.97
C ₁₄ -H ₃₁	1.0941	1.1339	1.0943	C ₁₃ -C ₁₄ -C ₁₅	111.88	111.80	111.51
C ₁₅ -C ₂₀	1.4038	1.4015	1.3995	C ₁₃ -C ₁₄ -H ₃₁	108.48	108.03	108.49
C ₁₅ -C ₁₆	1.4005	1.3984	1.4016	C ₁₅ -C ₁₄ -H ₃₁	106.32	107.63	106.47
C ₁₉ -C ₂₀	1.3912	1.3927	1.3946	C ₁₄ -C ₁₅ -C ₂₀	120.52	119.00	121.02
C ₁₈ -C ₁₉	1.3939	1.3982	1.3894	C ₁₄ -C ₁₅ -C ₁₆	120.71	121.81	120.55
C ₁₇ -C ₁₈	1.3940	1.3973	1.3895	C ₈ -C ₁₃ -C ₁₂	120.07	121.81	119.87
C ₁₆ -C ₁₇	1.3911	1.3936	1.3956	C ₁₇ -C ₁₈ -C ₁₉	121.76	120.48	121.86
C ₈ -C ₁₃	1.3588	1.3673	1.3587	C ₁₈ -C ₁₉ -C ₂₀	118.54	119.54	118.72
C ₁₃ -C ₁₄	1.5209	1.5001	1.5218	C ₁₅ -C ₂₀ -C ₁₉	121.16	120.60	121.18
C ₁₂ -C ₁₃	1.4691	1.4681	1.4685	C ₁₆ -C ₁₇ -C ₁₈	118.0	119.48	118.50
N ₁ -C ₈	1.3863	1.3970	1.3870	C ₁₅ -C ₁₆ -C ₁₇	120.99	120.71	121.30

The observed and calculated frequencies using DFT B3LYP/6-31G and probable assignments of 3d, 3f and 3h are summarized in Table 4. The C=C stretching bands appear at 1480-1640 cm⁻¹ in the infrared spectrum. The bands occurring at 1360, 1370 and 1367 cm⁻¹ in 3d, 3f and 3h, respectively in IR are assigned to the C–N stretching vibrations. The C=O stretching bonds is observed at 1643, 1651 and 1653 in 3d, 3f and 3h, respectively. The aromatic C–H stretching vibrations in 3d, 3f and 3h are observed at 3070, 3020 and 3047 cm⁻¹, respectively. The bands observed in the infrared spectra of 3d, 3f and 3h at 3384, 3440 and 3355 cm⁻¹ are assigned to the N–H stretching vibrations. The asymmetric and symmetric stretching vibrations of the nitro group are the most intense bands of the spectrum. The frequencies observed at 1540 cm⁻¹ in the infrared spectrum are assigned to the –NO₂ asymmetric stretching modes

of 3d. The very strong symmetric stretching vibration of nitro group of the compound is assigned to the wave number 1342 cm⁻¹ in the infrared spectra. The C-Cl absorption is observed in the broad region between 850 and 550 cm⁻¹. The very strong band in IR at 720 cm⁻¹ and 650 cm⁻¹ are to the C-Cl and C-F stretching of 3f and 3h, respectively. The correction factors used to correlate the experimentally observed and theoretically computed frequencies for each vibrational modes of 3d, 3f and 3h under DFT-B3LYP method is similar. The linear regression between the experimental and theoretical wave number of 3d, 3f and 3h are shown in Figures 5-7. Thus, vibrational frequencies calculated by using the B3LYP functional with 6-31G basis sets can be utilized to eliminate the uncertainties in the fundamental assignments in infrared vibration spectra.

Figure 5. A plot of experimental and theoretical IR of 3d at the B3LYP/6-31G(d) level.

Table 4. The observed FTIR, FT-Raman and calculated frequencies using B3LYP/6-31G(d) force field.

Assignment	3d		3f		3h	
	calcd.	Exp.	Calcd.	Exp.	Calcd.	Exp.
ν N-H	3326.1348	3384	3299.3526	3440	3341.8726	3355
ν C-H(aromatic)	3086.6595	3070	3075.6049	3020	3098.8765	3047
ν C-H(aliphatic)	3077.0829	2956	3074.5208	2975	2987.6543	2958
ν C=O	1643.9472	1643	1651.4347	1650	1657.8798	1653
ν NO ₂	1347.3871	1342	-	-	-	-
ν NO ₂	1540.8131	1540	-	-	-	-
ν C=C	1643.9472	1640	1622.4851	1620	1633.3451	1625
ν C=C	1622.4582	1620	1618.6870	1612	1610.4565	1612
ν C=C	1499.3334	1500	1596.1266	1600	1609.6767	1594
ν C=C	1479.6697	1480	1479.5006	1480	1501.8921	1498
ν C-N	1359.7844	1360	1359.8949	1370	1359.9831	1367
ν C-Cl	-	-	704.6949	720	-	-
ν C-F	-	-	-	-	661.2345	650
β HCC	1136.9538	1130	1076.6673	1080	1034.9823	1030
β HCC	1206.0126	1220	1142.5954	1140	1141.5672	1147
β HCC	1465.5443	1460	1205.4971	1210	1230.5123	1211
γ C-H	850.4244	840	851.5648	850	890.4352	891

^a ν -stretching; β -in-plane bending; γ -out of plane bending, wave numbers (cm⁻¹)

Figure 6. A plot of experimental and theoretical IR of 3f at the B3LYP/6-31G(d) level.

Figure 7. A plot of experimental and theoretical IR of 3h at the B3LYP/6-31G(d) level.

The ^1H and ^{13}C theoretical and experimental chemical shifts, isotropic shielding tensors and assignments of 3d, 3f and 3h are presented in Table 5 and Table 6, respectively. Aromatic carbons give signals in overlapped areas of the spectrum, with chemical shift values from 100 to 150 ppm in ^{13}C NMR, and 6-8.5 ppm in ^1H NMR spectra of 3d, 3f and 3h.

Table 5. The experimental and calculated ^1H isotropic chemical shifts (ppm) with respect to TMS of 3d, 3f and 3h.

Assignment	3d		3f		3h	
	Calcd.	Exp.	Calcd.	Exp.	Calcd.	Exp.
$\text{H}_{34}, \text{H}_{35}, \text{H}_{36}$	0.39	0.87	0.88	1.03	0.88	0.98
$\text{H}_{37}, \text{H}_{38}, \text{H}_{39}$	0.44	0.87	0.96	1.03	0.96	0.98
$\text{H}_{47}, \text{H}_{48}, \text{H}_{49}$	0.46	1.02	1.08	1.15	1.08	1.10
$\text{H}_{44}, \text{H}_{45}, \text{H}_{46}$	0.5	1.02	1.34	1.15	1.34	1.10
$\text{H}_{42}, \text{H}_{43}$	1.5	2.04	2.02	2.18	2.02	2.16
$\text{H}_{50}, \text{H}_{51}$	1.52	2.15	2.14	2.22	2.14	2.22
$\text{H}_{40}, \text{H}_{41}$	1.53	2.26	2.18	2.28	2.18	2.28
$\text{H}_{32}, \text{H}_{33}$	1.54	2.34	2.18	2.31	2.18	2.34
H_{31}	4.31	5.05	5.41	5.51	4.25	5.09
H_{54}	6.72	7.44	6.48	7.20	7.08	6.90
H_{52}	7.23	7.44	6.59	7.20	6.68	6.90
H_{55}	7.51	7.98	6.74	7.32	6.02	7.30
H_{53}	7.46	7.98	7.61	7.32	6.11	7.30

Table 6. The experimental and calculated ^{13}C isotropic chemical shifts (ppm) with respect to TMS of 3d, 3f and 3h.

Assignment	3d		3f		3h	
	Calcd.	Exp.	Calcd.	Exp.	Calcd.	Exp.
C_8	134.08	146.3	136.75	149.7	132.85	143.0
C_{13}	106.8	109.25	106.78	113.3	108.05	113.3
C_2	133.68	146.3	134.63	149.7	133.18	143.0
C_3	107.07	109.25	108.32	113.3	107.78	113.3
C_7	36.64	32.9	39.56	33.0	36.73	33.0
C_6	30.06	29.9	27.16	30.0	30.26	30.0
C_5	44.06	34.9	46.82	41.1	44.2	41.0
C_4	178.19	195.6	180.86	196.4	177.99	196.5
C_{24}	27.1	27.4	33.8	27.5	27.18	27.4
C_{23}	20.77	27.4	26.51	27.5	20.91	27.4
C_{14}	34.21	51.0	30.83	51.2	32.76	51.3
C_{15}	144.62	154.9	132.68	145.6	132.73	129.7
C_{20}	115.77	123.5	124.23	145.6	116.57	115.0
C_{19}	113.52	112.3	119.43	129.9	104.55	107.2
C_{18}	135.07	149.8	123.99	132.0	150.25	149.9
C_{17}	113.19	112.3	118.09	129.9	104.34	107.2
C_{16}	122.7	123.5	115.94	145.6	123.31	115.0
C_{12}	178.42	195.6	180.13	196.4	178.12	196.5
C_{11}	43.95	34.9	46.73	41.1	44.2	41.0
C_{10}	29.91	29.9	27.14	30.0	30.22	30.0
C_9	36.59	32.9	39.65	33.0	36.7	33.0
C_{21}	27.04	27.4	33.47	27.5	27.14	27.4
C_{22}	20.63	27.4	25.27	27.5	20.78	27.4

Due to the influence of electronegative atom, the chemical shift value of C_2 , C_8 and C_{18} in 3d, 3f and 3h are differ significantly in the shift positions in the range 123-150 ppm and the corresponding values of chemical shifts related to C_2 , C_8 and C_{18} are 133.68, 134.08 and 135.07 in 3d, 134.63, 136.75 and 123.99 in 3f and 133.18, 132.85 and 150.25 ppm in 3h, respectively. The higher chemical shift of C_{18} in 3d, 3f and 3h is due to the attachment of electron withdrawing nitro, Cl and F group at C_{18} . A down field shift is observed for C_2 compared with C_3 in 3d, 3f and 3h. That is due to the mesomeric effect between C_2 - C_3 - C_4 - O_{25} . The benzylic and allylic C-H carbon atom is calculated at 34.21, 30.83 and 32.76 in relatively good accordance with experimental results in 3d, 3f and 3h. Similarly, the benzylic and allylic C-H proton appear at 4.31, 5.41 and 4.25 ppm, in according to their resonated chemical shift. The down field signals at 7.51 and 7.46 in 3d, 6.74 and 7.61 in 3f and 6.68 and 7.08 ppm in 3h are assigned to H_{53} and H_{55} protons, respectively. This strongly indicates the electron withdrawing nature of NO_2 , Cl and F in their neighbourhood. The electron withdrawing nitro group cause deshielding of the aromatic protons H_{53} and H_{55} more than Cl and F. The calculated and experimental chemical shift values given in Table 5 and 6, show a good agreement. The linear regressions of the experimental and theoretical 1H and ^{13}C NMR Chemical shifts of 3a-c are represented in Figures 8-10.

a

b

Figure 8. A plot of experimental and theoretical a) 1H NMR and b) ^{13}C NMR chemical shifts of 3d at the B3LYP/6-31G(d) level.

a

b

Figure 9. A plot of experimental and theoretical a) 1H NMR and b) ^{13}C NMR chemical shifts of 3f at the B3LYP/6-31G(d) level.

a

b

Figure 10. A plot of experimental and theoretical a) 1H NMR and b) ^{13}C NMR chemical shifts of 3h at the B3LYP/6-31G(d) level.

5. ACKNOWLEDGEMENT

We thank the Research Committee of Islamic Azad University of Rasht Branch for partial support given to this study.

6. CONCLUSIONS

Finally, we develop an efficient and convenient procedure for the synthesis

of 1, 4- dihydropyridines through the three component synthesis of aldehydes, dimedone and ammonium acetate over nano-Fe₃O₄. This procedure offer advantages such as reduced reaction time, and higher yield, ease of execution and economic viability of the catalyst. This simple process combined with easy recovery and reuse of the catalyst make this procedure economic, benign and a waste free chemical process for the synthesis of dihydropyridines.

Selected structural parameters of the optimized geometries of the compounds have been obtained from DFT calculations. The vibration frequencies of the fundamental modes of the compound have been precisely assigned and analyzed and the theoretical results were compared with the experimental vibrations. ¹H and ¹³C NMR isotropic chemical shifts were calculated and the assignments are compared with the experimental values. The present investigation provides complete vibration assignments, structural information and NMR chemical shifts of these compounds.

REFERENCES

- Shan, R. Velazquez, C. Knaus, E.E. *J. Med. Chem.* **47**, 254, (2004).
- Manhold, R. Jablonka, B. Voigt, W. Schoenafinger, K. Schraun, K. *Eur. J. Med. Chem.* **27**, 229, (1992).
- Legeay, J. C. Eynde, J. J. V. Bazureau, J. P. *Tetrahedron* **63**, 12081, (2007).
- Love, B. Sander, K. M. *J. Org. Chem.* **30**, 1914, (1965).
- Agarwal, A. Chauhan, P. M. S. *Tetrahedron Lett.* **46**, 1345, (2005).
- Sridhar, R. Perumal, P.T. *Tetrahedron* **61**, 2465, (2005).
- Moseley, J. D. *Tetrahedron Lett.* **44**, 4129, (2003).
- Sabitha, G. Reddy, G. S. K. K. Reddy, Ch. S. Yadav, J. S. *Tetrahedron Lett.* **44**, 4129, (2003).
- Wang, L.-M. Sheng, J. Zhang, L. Han, J.-W. Fan, Z. Tian, H. Qian, C.-T. *Tetrahedron* **61**, 1539, (2005).
- Ko, S. Sastry, M. N. V. Lin, C. Yao, C, -F. *Tetrahedron Lett.* **46**, 5771, (2005).
- Ko, Sh. Yao, Ch. -F. *Tetrahedron*. **62**, 7293, (2006).
- W. Koch and M.C. Holthausen, A Chemist's Guide to Density Functional Theory, second ed., Wiley-VCH Verlag GmbH, Weinheim, 2001.
- Becke, A. D. *J. Chem. Phys.* **98**, 5648, (1993).
- Lee, C. Yang, W. Parr, R.G. *Phys. Rev. B* **37**, 785, (1988).
- Zhao, Y. Gonzalez-Garcia, N. Truhlar, D.G. *J. Phys. Chem. A* **109**, 2012, (2005).
- Nikpassand, M. Mamaghani, M. Tabatabaieian, K. Kupaei Abiaz, M. *Mol. Diversity* **389**, (2009).
- Zare, L. Nikpassand, M. *Chin. Chem. Lett.* **22**, 531, (2011).
- Nikpassand, M. Zare, L. Saberi, M. *Monatsch. Chem.* (in press)
- Frisch, M. J. Trucks, G.W. Schlegel, H.B. Scuseria, G.E. Robb, M.A. Cheeseman, J.R. Montgomery J.A. Vreven, T. Kudin, K.N. Burant, J.C. Millam, J.M. Iyengar, S.S. Tomasi, J. Barone, V. Mennucci, B. Cossi, M. Scalmani, G. Rega, N. Petersson, G.A. Nakatsuji, H. Hada, M. Ehara, M. Toyota, K. Fukuda, R. Hasegawa, J. Ishida, M. Nakajima, T. Honda, Y. Kitao, O. Nakai, H. Klene, M. Li, X. Knox, J.E. Hratchian, H.P. Cross, J.B. Adamo, C. Jaramillo, J. Gomperts, R. Stratmann, R.E. Yazyev, O. Austin, A.J. Cammi, R. Pomelli, C. Ochterski, J.W. Ayala, P.Y. Morokuma, K. Voth, G.A. Salvador, P. Dannenberg, J.J. Zakrzewski, V.G. Dapprich, S. Daniels, A.D. Strain, M.C. Farkas, O. Malick, D.K. Rabuck, A.D. Raghavachari, K. Foresman, J.B. Ortiz, J.V. Cui, Q. Baboul, A.G. Clifford, S. Cioslowski, J. Stefanov, B.B. Liu, G. Liashenko, A. Piskorz, P. Komaromi, I. Martin, R.L. Fox, D.J. Keith, T. Al-Laham, M.A. Peng, C.Y. Nanayakkara, A. Challacombe, M. Gill, P.M.W. Johnson, B. Chen, W. Wong, M.W. Gonzalez, C. Pople, J.A. Gaussian03, Revision B.03, Gaussian, Inc., Pittsburgh, PA, 2003.