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A convenient, green, solvent free synthesis and characterization of novel fluoro chalcones under grind-stone chemistry

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ABSTRACT

A series of (E)-3-[4-(Difluoromethoxy)-3-hydroxyphenyl]-1-phenylprop-2-en-1-ones were synthesized by simple solvent-free grinding technique and conventional method. The effectiveness of synthesis under grinding condition is demonstrated using a broad spectrum of acetophenones with 4-difluoromethoxy-3-hydroxybenzaldedye in presence of base. The synthesized compounds were characterized by FT-IR, LC-MS, ^{1}H NMR, ^{13}C NMR and mass spectra. The HSQC correlation spectrum is analyzed for (E)-3-[4-(Difluoromethoxy)-3-hydroxyphenyl]-1-phenylprop-2-en-1-one.

Keywords: Green Chemistry, solvent-free, grinding, fluoro chalcones, H-F and C-F coupling constant.

INTRODUCTION

Green Chemistry (GC) has become a powerful tool in organic chemistry in the last decade and especially in recent years [1-2]. The avoidance of solvents in chemical processes, or the replacement of hazardous solvents with more benign solvents, such as water[3-4], ionic liquid[5], have become major concerns in academic research (academia) and industry, and the need for green(er) reactions is now globally accepted. The solvent-free multicomponent[6]syntheses are particularly attractive, because they incorporate many green chemistry principles. The α,β-unsaturated ketones 1,3-diarylprop-2-en-1-ones called as chalcones. The chalcones are synthesized by Claisen-Schmidt condensation of an arylaldehyde with aryl methyl ketone. The reason that organic chemists are interested to synthesize chalcone is simple. Chalcone and its derivatives, among the large families of plant constituents, have various therapeutic benefits including antimicrobial[7], anti-inflammatory[8], antitumor[9], antiulcerative[10],antifungal[11], antibacterial[12], anticancer[13], and anti-HIV[14] properties. Chalcone are important starting materials for the syntheses of different classes of heterocyclic compounds such as flavonoids[15], isoflavonoids[16], pyrazole[17], pyrimidine[18-19]and etc[20-22]. The fluorinated drugs play major role in the present pharmaceutical market. Fluorinated drugs are used for treatment of diseases of the central nervous system (CNS), various cardiovascular diseases and obesity, anti-cancer, antibacterial agents, and antifungal therapy [23-24].Fluorine atoms are useful in providing connectivity information in carbon NMR spectrum due to its long-range spin-spin coupling constant [25]. There are varieties of methods available to synthesis chalcone among this; solvent-free grinding technique is simple, easy work up, high yield, convenient and requires no special apparatus. Toda *et al*[26]first introduces grind stone chemistry in 1987. The reactions are initiated by grinding, with the transfer of very small amount of energy through friction. There are several organic transformations has been reported in grind stone chemistry such as, Biginelli reaction[27], one-pot synthesis of spiro-indolinetriones[28], Cannizzaro reaction[29], Aldol condensation[30-31]and Knoevenagel condensation[32].

MATERIALS AND METHODS

2.1. Experimental section.

The purity and completion of reaction was monitored by TLC. The melting points were recorded in open capillaries and are uncorrected. The FT-IR spectra were recorded on a AVATAR-330FT-IR spectrophotometer. The sample was mixed with KBr and pellet technique was adopted to record the spectra in cm^{-1}. ^1H NMR spectra were recorded at 400 MHz on BRUKER AV-III or Varian 400 MHz spectrometer using $CDCl_3$or DMSO-d_6 as solvent and TMS as internal standard. ^{13}C NMR spectra were recorded at 100 MHz on BRUKER AV-III spectrometer in $CDCl_3$. For recording ^1H NMR spectra, solution were prepared by dissolving about 10 mg of the compound in 0.5 mL of $CDCl_3$or DMSO-d_6.While for recording ^{13}C NMR spectra, about 50 mg of the compound was dissolved in the same volume of the solvent. Mass spectra were recorded on SCIEX-API 2000.

2.2. General procedure for preparing (E)-3-[4-(Difluoromethoxy)-3-hydroxyphenyl]-1-phenylprop-2-en-1-ones

Conventional method:

A solution of sodium hydroxide 2mL (10%) in water and 10 mL of rectified spirit is placed in a 250 mL bolt-head flask provided with a mechanical stirrer. The flask is immersed in a bath of crushed ice. The appropriate acetophenone (5mmol) and appropriate benzaldehyde (5mmol) are added. The temperature of the mixture is maintained at about 20ºC stirred vigorously until the mixture is so thick that stirring is no longer effective (1h). The stirrer was removed and the reaction mixture was neutralized with dilute HCl and kept in the refrigerator overnight. The product was filtered and washed with cold water. It is further washed with zone of ice-cold rectified spirit.

Grinding method:

A mixture of 4-difluoromethoxy-3-hydroxybenzaldedye (5mmol), respective substituted acetophenones (5mmol)and sodiumhydroxide was ground together in mortar with pestle for 5 min and left to harden at room temperature for 30 min. The solid was dissolved in cold distilled water and acidified with dilute HCl and kept aside for overnight. The solid that separated was filtered, dried and recrystallized from ethanol.

2.2.1*(E)-3-[4-(Difluoromethoxy)-3-hydroxyphenyl]-1-phenylprop-2-en-1-one*

FT-IR(KBr, cm^{-1}): 3338 (OH), 3063-3013 (Aromatic C-H), 2920-2849 (Aliphatic C-H), 1657 (C=O); ^1H NMR(DMSO-d_6, 400 MHz, ppm): δ = 10.16 (broad singlet, 1H, OH), 7.15 (t, 1H, H-7), 7.64 (d, 1H, H-9), 7.79 (d, 1H, H-8), 8.13-7.18 (aromatic); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm): δ = 189.10 (Carbonyl C-10),122.59 (C-9), 143.45 (C-8), 116.42 (C-7), 117.40-184.74 (aromatic);Mass (m/z): 291 (M+1).

2.2.2*(E)-3-(4-(difluoromethoxy)-3-hydroxyphenyl)-1-(4-fluorophenyl)prop-2-en-1-one*

FT-IR(KBr, cm^{-1}): 3311 (OH), 3059-3011(Aromatic C-H), 2921-2852 (Aliphatic C-H), 1654 (C=O); ^1H NMR($CDCl_3$, 400 MHz, ppm): δ = 5.64 (broad singlet, 1H, OH), 6.59 (t, 1H, H-7), 7.71 (d, 1H, H-9), 7.43 (d, 1H, H-8), 8.06-7.09 (aromatic); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm): δ = 188.65 (Carbonyl C-10), 122.08 (C-9), 143.69 (C-8), 115.97 (C-7), 115.75-167.00 (aromatic); Mass (m/z): 307 (M-1).

2.2.3*(E)-1-(4-chlorophenyl)-3-(4-(difluoromethoxy)-3-hydroxyphenyl)prop-2-en-1-one*

FT-IR(KBr, cm^{-1}): 3413 (OH), 3095-3063 (Aromatic C-H), 2915-2843 (Aliphatic C-H), 1664 (C=O); ^1H NMR($CDCl_3$, 400 MHz, ppm): δ = 5.59 (broad singlet, 1H, OH), 6.59 (t, 1H, H-7), 7.72 (d, 1H, H-9), 7.50 (d, 1H, H-8), 7.97-7.16 (aromatic); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm): δ = 188.07 (Carbonyl C-10), 121.69 (C-9), 143.72 (C-8), 116.39 (C-7), 117.41-148.69 (aromatic); Mass (m/z): 325 (M+1).

2.2.4*(E)-3-(4-(difluoromethoxy)-3-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one*

FT-IR(KBr, cm^{-1}): 3294 (OH),3063-3013 (Aromatic C-H), 2969-2844 (Aliphatic C-H),1653 (C=O); ^1H NMR($CDCl_3$, 400 MHz, ppm): δ = 5.71 (broad singlet, 1H, OH), 6.58(t, 1H, H-7), 7.72 (d, 1H, H-9), 7.47 (d, 1H, H-8), 3.89 (s, 3H, OC**H**$_3$), 8.04-6.92 (aromatic); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm): δ = 188.49 (Carbonyl C-10), 122.45 (C-9), 142.58 (C-8), 116.03 (C-7), 113.94-163.60 (aromatic), 55.55 (O**C**H$_3$); Mass (m/z): 321 (M+1).

2.2.5*(E)-3-(4-(difluoromethoxy)-3-hydroxyphenyl)-1-(4-nitrophenyl)prop-2-en-1-one*

FT-IR(KBr, cm-1): 3321(OH), 3123(Aromatic C-H), 2922-2853 (Aliphatic C-H), 1657 (C=O); ^1H NMR($CDCl_3$, 400 MHz, ppmδ = 5.65 (broad singlet, 1H, OH), 6.60(t, 1H, H-7), 7.75 (d, 1H, H-9), 7.41 (d, 1H, H-8), 8.37-7.18 (aromatic); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm): δ = 188.34 (Carbonyl C-10), 121.82 (C-9), 144.77 (C-8), 116.39 (C-7), 117.60-149.80 (aromatic); Mass (m/z): 334 (M-1).

2.2.6*(E)-1-(4-bromophenyl)-3-(4-(difluoromethoxy)-3-hydroxyphenyl)prop-2-en-1-one*
FT-IR(KBr, cm^{-1}):3338 (OH), 3056(Aromatic C-H), 2923-2849 (Aliphatic C-H), 1656 (C=O); ^{1}H NMR(DMSO-d_6, 400 MHz, ppm): δ = 10.43 (broad singlet, 1H, OH), 7.07(t, 1H, H-7), 7.71 (d, 1H, H-9), 7.61 (d, 1H, H-8), 8.03-7.16 (aromatic); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm): δ = 188.23 (Carbonyl C-10), 121.67 (C-9), 143.73 (C-8), 116.40 (C-7), 117.48-148.70 (aromatic); Mass (m/z): 369 (M+1).

2.2.7*(E)-3-(4-(difluoromethoxy)-3-hydroxyphenyl)-1-(3-nitrophenyl)prop-2-en-1-one*
FT-IR(KBr, cm^{-1}): 3385 (OH), 3084 (Aromatic C-H), 2922-2860 (Aliphatic C-H), 1660 (C=O); ^{1}H NMR($CDCl_3$, 400 MHz, ppmδ = 5.65 (broad singlet, 1H, OH), 6.61(t, 1H, H-7), 7.80 (d, 1H, H-9), 7.45 (d, 1H, H-8), 8.83-7.17 (aromatic); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm): δ = 187.79 (Carbonyl C-10), 123.30 (C-9), 145.34 (C-8), 115.90 (C-7), 116.11-148.47 (aromatic); Mass (m/z): 334 (M-1).

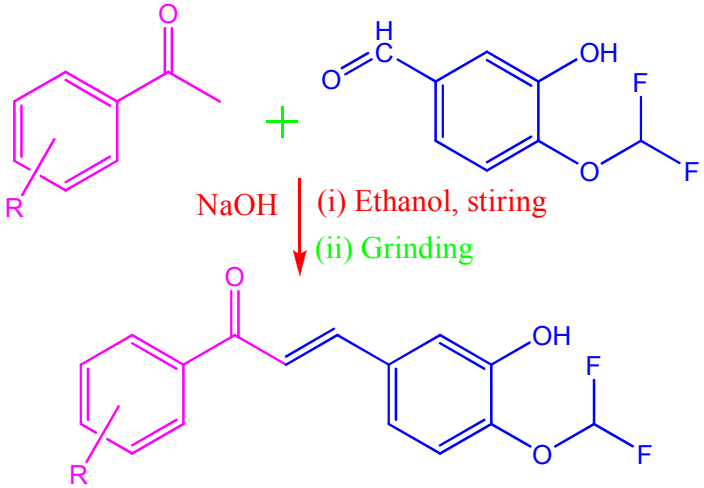
2.2.8*(E)-3-(4-(difluoromethoxy)-3-hydroxyphenyl)-1-p-tolylprop-2-en-1-one*
FT-IR(KBr, cm^{-1}): 3346 (OH), 3050 (Aromatic C-H), 2922-2857 (Aliphatic C-H), 1658 (C=O); ^{1}H NMR($CDCl_3$, 400 MHz, ppm): δ = 5.91 (broad singlet, 1H, OH), 6.59 (t, 1H, H-7), 7.71 (d, 1H, H-9), 7.47 (d, 1H, H-8), 7.78-6.49 (aromatic), 21.15 (**C**H_3); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm): δ = 188.50 (Carbonyl C-10), 122.02 (C-9), 142.85 (C-8), 116.43 (C-7), 117.36-148.77 (aromatic), 21.15 (**C**H_3); Mass (m/z): 305 (M+1).

2.2.9*(E)-3-(4-(difluoromethoxy)-3-hydroxyphenyl)-1-(2,4-dimethoxyphenyl)prop-2-en-1-one*
FT-IR(KBr, cm^{-1}): 3310(OH), 3019 (Aromatic C-H), 2920-2843 (Aliphatic C-H), 1650 (C=O); ^{1}H NMR($CDCl_3$, 400 MHz, ppm): δ = 5.81 (broad singlet, 1H, OH), 6.56(t, 1H, H-7), 7.59 (d, 1H, H-9), 7.46 (d, 1H, H-8), 7.78-6.49 (aromatic), 3.87 (OC**H$_3$**), 3.91 (OC**H$_3$**);^{13}C NMR (DMSO-d_6, 100 MHz, ppm): δ = 190.39 (Carbonyl C-10), 121.24 (C-9), 140.83 (C-8), 116.04 (C-7), 98.66-164.51 (aromatic), 55.79 (OCH_3), 55.61(O**C**H_3); Mass (m/z): 351 (M+1).

2.2.10*(E)-3-(4-(difluoromethoxy)-3-hydroxyphenyl)-1-(naphthalen-1-yl)prop-2-en-1-one*
FT-IR(KBr, cm^{-1}): 3348 (OH), 3013 (Aromatic C-H), 2924-2849 (Aliphatic C-H), 1657 (C=O); ^{1}H NMR(DMSO-d_6, 400 MHz, ppm): δ = 10.15 (broad singlet, 1H, OH), 7.14(t, 1H, H-7), 7.51(d, 1H, H-9), 7.41 (d, 1H, H-8),8.31-7.17 (aromatic); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm): δ = 194.03 (Carbonyl C-10), 124.91 (C-9), 144.15 (C-8), 116.39 (C-7), 116.90-148.74 (aromatic).

RESULTS AND DISCUSSION

In the present solvent-free method, the effectiveness of synthesis under grinding condition is demonstrated using a broad spectrum of acetophenones with4-difluoromethoxy-3-hydroxybenzaldedye.The chalcones (**Fig.1**) were prepared by the Claisen-Schmidt condensation using both conventional as well as grinding methods (**Scheme 1**).



Scheme1. Synthetic route of chalcone

In order to demonstrate the efficiency and the applicability of grind method, we performed the reaction with a variety of aryl methyl ketone with aldehyde under solvent-free grinding method and conventional method (Table 1).

The conventional synthesis of chalcones involves the condensation of substituted acetophenone with 4-difluoromethoxy-3-hydroxybenzaldedye in ethanol in presence of sodium hydroxide.

Table 1. Analytical data of compounds 3- 12

Entry	R	M.P (°C)	Yield (%)	
			conventional	Grinding
3	H	152-154	70	86
4	F	114-116	75	88
5	Cl	162-164	80	90
6	OCH_3	132-134	85	92
7	NO_2	134-136	55	87
8	Br	142-144	82	90
9	2-NO_2	118-120	50	85
10	CH_3	166-168	78	88
11	2,4-OCH_3	144-146	85	90
12	Napthyl	136-138	60	90

Table 2.Hydrogen-Fluorine ($^2J_{H-F}$) and Carbon-Fluorine ($^1J_{C-F}$) coupling constants values

Entry	^{1}H NMR	^{13}C NMR
	$^2J_{H-F}$Hz	$^1J_{C-F}$ Hz
3	74	257
4	73	263
5	74	257
6	73	261
7	73	257
8	74	257
9	73	263
10	74	257
11	73	261
12	75	256

The 4-difluoromethoxy-3-hydroxybenzaldedye and acetophenone mixture is colorless liquids at room temperature [**Fig. 2, (i)**]. After the addition of the NaOH the liquids immediately turn greenish yellow indicating the formation of the enolate[**Fig. 2,(ii)**]. By aggregating the reaction mixture using a mortar and pestle, the viscosity rapidly increases to form a tacky solid after 5 min of constant mixing[**Fig. 2, (iii)**]. The pliable solid can be left to harden [**Fig. 2, (iv)**] as the solid product. After 30 min, resulting in the formation of sodium adduct **3** as an amorphous powder [**Fig. 2, (v)**]. Then the sodium adduct was dissolved in cold distilled water and neutralized with dilute HCl gave desired chalcone as crude product [**Fig. 2, (vi)**], filtered, dried and recrystallized in ethanol. These solvent-free Claisen-Schmidt condensations proceed clean and simple.

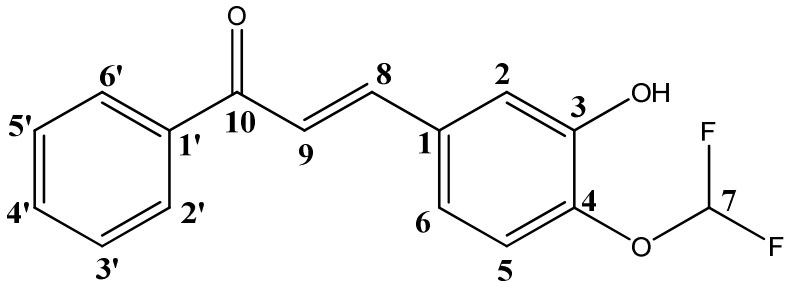


Fig.1. Representative Structure of compound

It is obvious that effects of grinding method observed, and the products were obtained in good yields. A limitation of the reaction is observed for the chalcones with electron withdrawing group used in place of acetophenone. Using electron donating group instead of electron withdrawing gave the desired product in good yield.

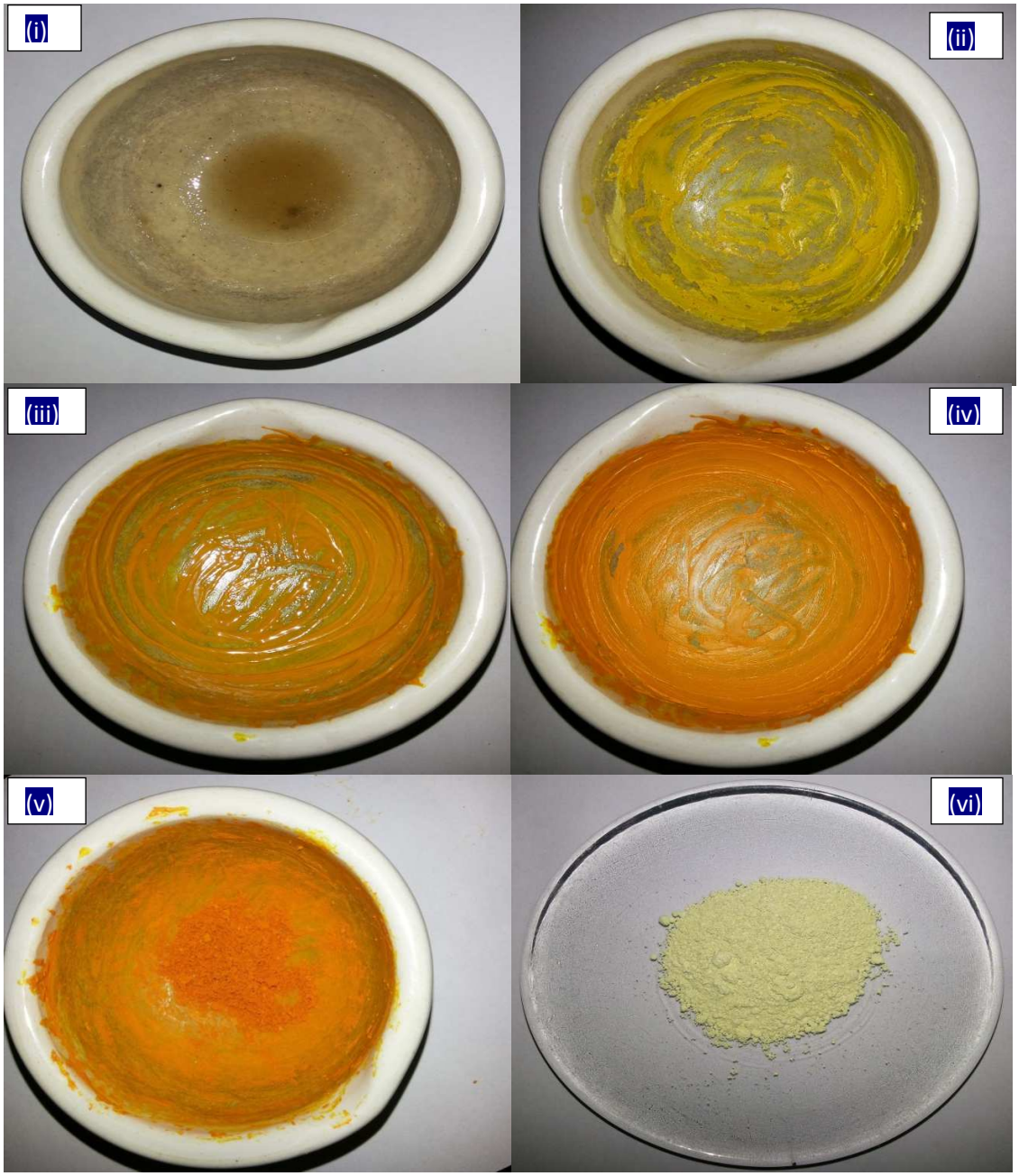


Fig.2. Photographic plates

It is obvious that effects of grinding method observed, and the products were obtained in good yields. A limitation of the reaction is observed for the chalcones with electron withdrawing group used in place of acetophenone. Using electron donating group instead of electron withdrawing gave the desired product in good yield.

*2.1. IR spectral analysis of compound **3***

In IR spectra of compound **3**, the presence of carbonyl stretching frequency at 1657 cm^{-1} confirms the formation of chalone. A collection of bands observed in the region of 3063-3013 cm^{-1} are due to aromatic C-H stretching frequency. The absorption bands appeared in the region of 2920-2849 cm^{-1} is assigned to aliphatic C-H stretching

frequencies. The C=C stretching frequency observed at 1604 cm^{-1}. The absorption frequency at 3338 cm^{-1} is corresponds to OH stretching group.

*2.2. NMR spectral analysis of compound **3***

^{1}H NMR:

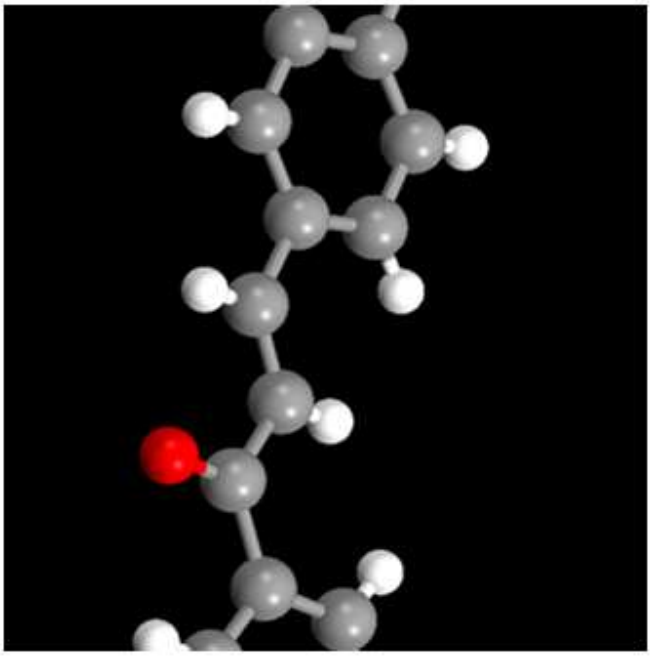
A broad singlet at 10.16ppm is due to hydroxyl proton. A doublet at 8.13ppm with the integral value of two is assigned to H-2' and H-6'protons *ortho* to carbonyl. There are two doublets centered at 7.79ppm and 7.64ppm corresponds to one proton each with coupling constant value of 15.6Hz and 16.0Hz are assigned to two protons on the carbon- carbon double bond H-8 and H-9 respectively. The coupling constant values suggest that the two adjacent protons H-8 and H-9 are *trans* to each other. So the product formed is *trans*chalcone *i.e. E* configuration. A triplet centered at7.57ppm corresponds to two protons is assigned to H-3' and H-5'. A peak centered at 7.40ppm with integral value of two is due to H-2 and H-6 protons. A doublet at 7.19ppm with integral value of one is assigned to H-5. A triplet centered at 7.15ppm corresponds to one proton with coupling constant value of 74.4Hz is due to H-7 proton, having *geminal* coupling with two fluorine atoms.

^{13}C NMR:

The signal at 190.34ppm is due to carbonyl carbon. The signals at 143.45ppm and 122.59ppm are assigned to methylene carbons C-8 and C-9 respectively. The signal at 115.99ppm observed as triplet is assigned to carbon bearing two fluorine atoms and one proton. This is due to two fluorine atoms *geminal* coupling with carbon atom ($^{1}J_{C\text{-}F}$).The signals appeared between 115.89-147.65ppm are aromatic carbons.

HSQC Spectrum:

In the HSQC spectrum of the compound, a triplet cantered at 7.15ppm having integral value of one, correlates with a triplet centered at 116.42ppm in ^{13}C NMR, suggests that the proton and the two fluorine atoms are attached to that carbon *i.e.*C-7. A doublet at 7.19ppm corresponds to one proton correlates with the signal at 121.22ppm is assigned to C-5. A peak centered at 7.40ppm with integral value of two correlates with the signals at 120.21ppm and 117.40ppm is assigned to C-6 and C-2 respectively. A triplet centered at 7.57ppm corresponds to two protons correlates with 128.78ppm is assigned to C-3' and C-5'. A doublet centered at7.64ppm correlates with 143.23ppm is due to C-9. Another doublet centered at7.79ppm is correlates with the signal at 122.01ppm are assigned to C-8. A doublet at 8.13ppm corresponding to two protons correlates at 128.45ppm is due to C-2' and C-6'. The signals at 189.10, 148.74, 140.45 and 132.79ppm don't show any correlation. The signal at 189.10ppm is due to carbonyl carbon and others are *ipso* carbons.



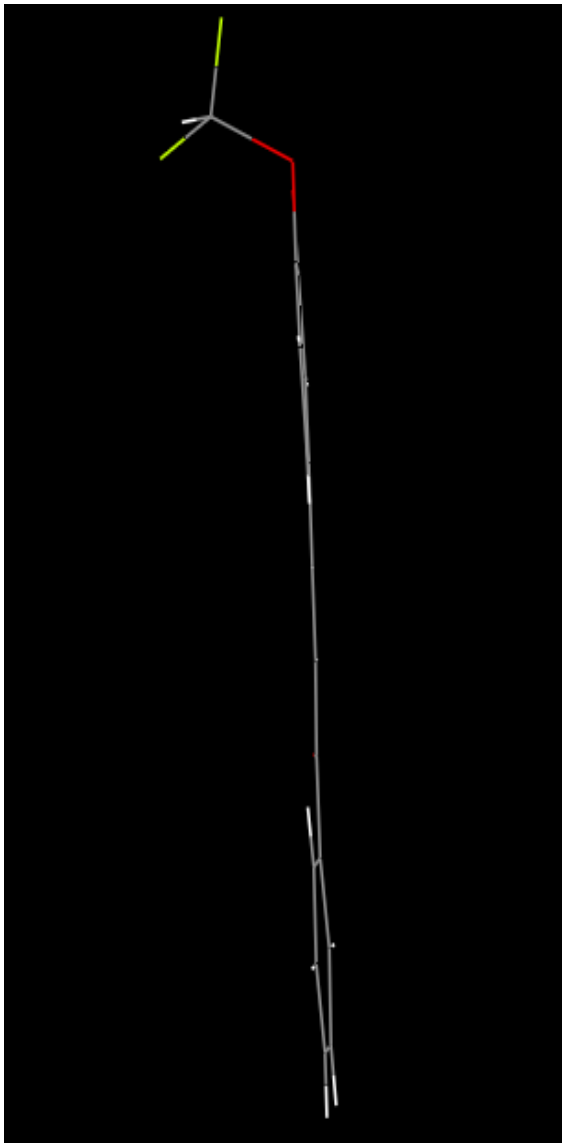


Fig.3.The structure of compound 3 in normal and windmill

Fluorine coupling:
The nuclear spin quantum number for fluorine is ½ and thus fluorine couples to proximate protons and carbons in a manner similar to hydrogen. The Hydrogen atom at C-7 had*geminal* coupling ($^{2}J_{H\text{-}F}$) with two fluorine atoms at C-7 gave a triplet at 6.99 ppm with coupling constant value of 54Hz in ^{1}H NMR. In ^{13}C NMR, a triplet is observed at 115.22 ppm with the coupling constant value of 58.22 Hz is due to C-7 have single bond ($^{1}J_{C\text{-}F}$) coupling with two fluorine atoms. The coupling constant values of chalcones**3-12** are given in**Table.2**.

*2.3.The single crystal X-ray structural analysis compound **3***
The compound **3** crystallizes in a monoclinic system with $P2_1/n$ space group[33].Unit cell contains four molecules with intermolecular interaction. The α,β-unsaturated keto group and two phenyl rings are almost same plane but the difluoromethoxy group substituted in phenyl ring is above this plane. And this look like the wind mill structure to the compound **3** as shown in **Fig.3**[34].

CONCLUSION

In conclusion, synthesis of chalcones was carried out in good yields form the condensation between 4-difluoromethoxy-3-hydroxybenzaldedye and various acetophenone in presence of sodiumhydroxide. The grind-stone, solvent-free procedure is carried out in a shorter reaction time and easier work-up and obtained a higher yield than conventional method.

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