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SUZUKI, HECK AND SONOGASHIRA REACTIONS: SYNTHESIS OF SOME NOVEL ISOXAZOLE DERIVATIVES

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ABSTRACT

The chalcone (E)-3-(4-ethoxyphenyl)-1-phenylprop-2-en-1-one (1) has been synthesized from available 4-fluoroacetophenone and 4-fluorobenzaldehyde in a basic medium. Compound (1) reacts with bromine in a glacial acetic acid to get (E)-2, 3-dibromo-3-(4-ethoxyphenyl)-1-phenylpropane-1-one (2). A cyclization of (2) with hydroxylamine hydrochloride in a basic medium furnished isoxazole derivative (3). Reaction of (3) with N-halosuccinimide in a glacial acetic acid afforded 3, 5-bis (4-fluorophenyl)-4-haloisoxazoles (4, 5), [halogen = Br (4), I (5)]. The halo-substituted isoxazoles (4, 5) were used as a key intermediate for the synthesis of novel substituted isoxazole derivatives (6-12) based on the Suzuki, Heck and Sonogashira reactions .The structures of the novel compounds were confirmed using the physical spectroscopy measurements like: FT-IR spectra, Mass spectra, ^{1}H, ^{13}C, ^{19}F-NMR spectra and micro elemental analysis (C. H. N).

KEYWORDS: Synthesis, Chalcone, Isoxazole Derivatives, Characterization

INTRODUCTION

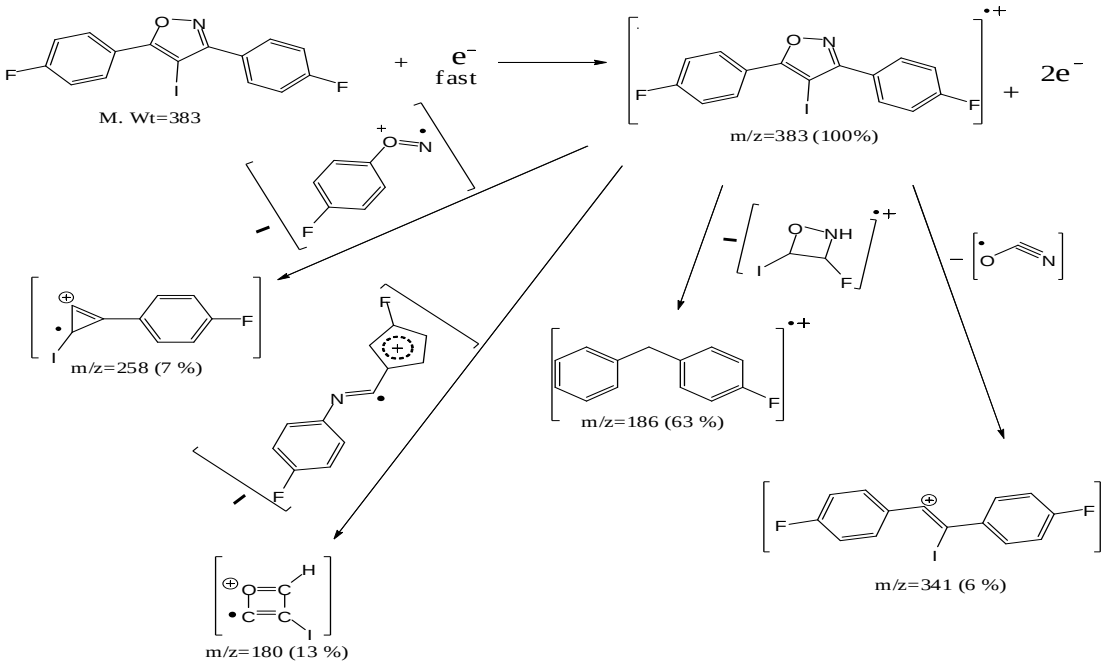
Isoxazoles derivatives have been considered as a magic moiety possessing myriad spectrum of medicinal activities [1]. In this research, we reported on the synthesis of substituted isoxazole derivatives based on the Suzuki, Heck and Sonogashira reactions starting from chalcone moiety with the purpose of investigating in the further their applications as antibacterial antifungal.

Derivatives of Isoxazole have played a crucial role in the history of heterocyclic chemistry and been used extensively important pharmacophores and synthons in the field of organic chemistry. Owing to their versatile chemotherapeutic importance, a significant amount of research effort has been focused on these nuclei. Isoxazole derivatives exhibit various biological activities such as, Antibacterial [2], Anticonvulsant [3], Anticancer [4], and Anthelmintics [5]. Antiinflammatory [6-7], Adenosine antagonist [8], Fungicidal [9], Herbicidal [10], Hypoglycemic [11], Muscle relaxant [12], Nematocidal [13], Insecticidal [14], Antiviral [15] and Antimicrobial [16].Isoxazoles are five membered heterocyclic compounds containing oxygen and nitrogen atom in the ring. They are medicinal and pharmaceutical important natural products. Numerous conventional and environmentally benign synthetic methods are reported for the isoxazoles synthesis. Under solvent-assisted or solvent-free conditions, chalcones also employed for deriving isoxazoles by cyclization with hydroxylamine hydrochloride in presence of catalysts. Cyclization of substituted phenyl and chalcones with hydroxylamine hydrochloride yields some novel aryl and indole based isoxazoles. Isoxazole derivatives possess many kinds of biological activities due to hetero atom O, N, double bond and polar group's presents in the ring [17]. Therefore, this work deals with the synthesis of the isoxazole derivatives from chalcones and screening their C - C Cross Coupling.

RESULTS AND DISCUSSIONS

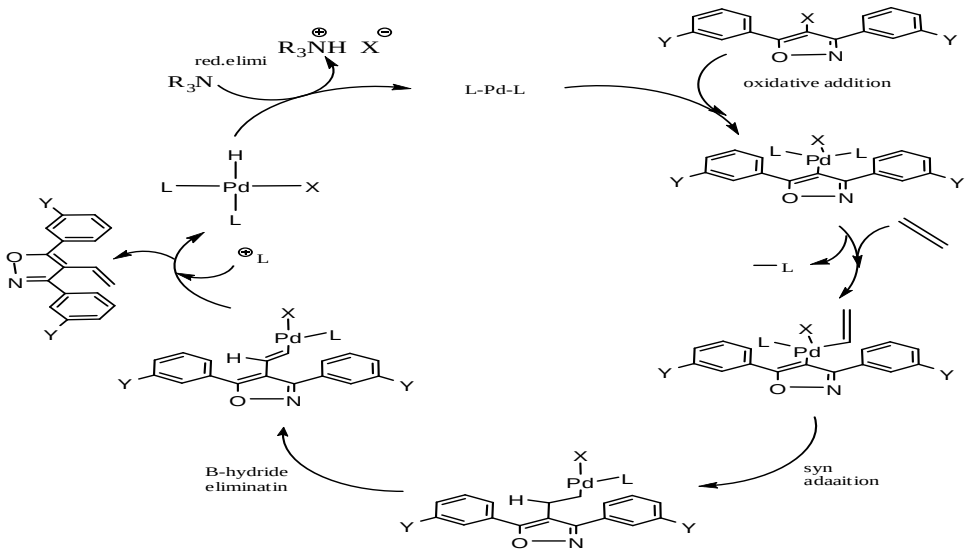
The present work describes the synthesis of some novel isoxazole derivatives starting from chalcone derivative (1) in Scheme (3).

The reported compounds in this paper correspond to the three major different reactions: Suzuki, Heck and Sonogashira which guide to synthesize novel isoxazole derivatives. The starting material (E)-1, 3-bis (4-fluorophenyl) prop-2-en-1-one (1) was synthesized according to a published method [18] in 93% yield. (E)-2,3-dibromo-1,3-bis(4-fluorophenyl)propan-1-one (2) was synthesized from the corresponding functionalized chalcone and bromine in a glacial acetic acid in 73% yield . Treatment of compound (2) with hydroxylamine hydrochloride in a basic medium led to get compound 3, 5-bis (4-fluorophenyl) isoxazole (3) in 66% yield. The new halo-isoxazoles (4, 5) were synthesized from the reaction of compound (3) with N-halo succinimide when [X= Br (4), I (5)] as a key intermediate in 75%, 82% yields, respectively. The mass spectrum of a compound [5] was demonstrated characteristic peaks at [m/z (100%): 180 (13%), 186 (63%), 258 (7%), 341 (6%), 383 (100%)]. The spectrum was showed a value of a molecular weight [$C_{15}H_8IF_2NO$: Calc., M.Wt =383; found, M.Wt=383.9698]. The proposed fragmentation as follows is shown in Scheme (1):



Scheme 1: The Proposed Fragmentation of Mass Spectrum for Compound (5)

It is interesting to note that iodoisoxazole (5) derivative gave high yields of the products (6-12) more than bromoisoxazole (4) derivative. Based on the Suzuki reaction, the halo-isoxazole derivatives (4, 5) were reacted with aryl boronic acid in the presence of palladium acetate to get the derivatives (6-9) in 54%, 64%, 52%, 60 % yields, respectively. The reaction between the halo-isoxazole derivatives (4,5) with butylacrylate or ethylvinyl ether in the presence of palladium acetate and tetrabutylammonium iodide guide to get (E)-ethyl-3,5-bis(4-fluorophenyl)isoxazol-4-yl)acrylate (10) or (E)-4-(2-ethoxyvinyl)-3,5-bis(4-fluoro phenyl)isoxazole (11) in 47% or 50 % yields based on the Heck reaction . The proposed mechanism for the formation of compounds (10, 11).



Scheme 2: The Mechanism Steps for the Synthesis of Compounds [10, 11]

On the other hand, the novel derivative 4-[3,5-bis(4-fluoro phenyl)isoxazol-4-yl]-2-methylbut-3-yn-2-ol (12) was synthesized from the halo compound (4,5) with 2-methyl-3-butyl-2-ol in trimethylamine in the presenece of cuprous iodide and palladium complex according to Sonogashira reaction in 78 % yield . All the physical spectral data were fitted with the structures of novel isoxazole derivatives.

EXPERIMENTAL

General

Initial Chemical Compounds was obtained from BDH, Merck and Fluka companies. Mellting points were determined in capillary tubes on Sturat Scientific melting point SMPLU-K and are uncorrected. Infrared spectra were recorded on Shimadzu FT-IR (8300) spectrophotometer by using KBr pellet technique. ^{1}H-NMR spectra was recorded on (Bruker DMX-500 NMR spectrophotometer) in frequency 400 and/or 60 MHz, using TMS as the internal standard in (DMSO-d_6). A mass spectrum was recorded on Ultra Shimadzu (GCHS-QP 2010).Also Elemental Analysis (C.H.N.S) for all new compounds were recorded in Jordan-Amman. The reactions were monitored by TLC on silica gel thin layer plates.

Synthesis of (E)-1, 3-bis (4-Fluorophenyl) Prop-2-en-1-One (1):

Dissolve 3.5 g of sodium hydroxide in 40 ml of water and add 25 ml of 95% ethanol in a bath of crushed ice pour in 0.08 mole of para substituted acetophenone and shake the mixture well. Then 0.08 mole of the different benzaldehyde is added at once. Allow the mixture to stand in the ice bath for one or two hour in freezer. Filter the product and wash with water, recrystallize the crude product from 95% ethanol. M. p (C°): 88-90, color: White, Yield: 92(%). IR: cm^{1}, 3074 (C-H) aromatic, 1603-1564 (C=C), 1661 (C=O), 1030 (C-F). ^{1}H-NMR: δ ppm 7.40 (d, 1H, CH-C=Ph), 7.74 (d, 1H, CH-C=O), 7.78-8.27 (m, 8H, C-H). ^{13}C-NMR: δ ppm 116 (H-C=Ph), 131 (H-C=O), 128-166 (aromatic Carbon ring), 188 (C=O). Anal. Calcd for $C_{15}H_{10}F_2O$: C, 73. 76; H, 4.13. Found C, 72.83; H, 3.43. %.

Synthesis of (E)-2, 3-Dibromo-1, 3-Bis (4-Fluorophenyl) Propan-1-one (2)

Place 0.023 moles of pure, dry chalcone (1) in a glacial acetic acid (HOAc) and add 0.023 moles of Br_2 (about 3.84 g Br_2 in 6.5 ml of a 20% solution in HOAc) dropwise during 30 min. Pour slowly 500 ml water to the reaction mixture, collect the solid dibromide, dried and recrystallize from ethanol and collected the white solid dibromide. M.p

(C˚): 131-133, color: White, Yield: 76 (%). IR: cm^{1}, 3110 (C-H) aromatic, 1672-1592 (C=C), 1682 (C=O), 722 (C-Br), 1219 (C-F). Anal. Calcd for $C_{15}H_{10}F_2Br_2O$: C, 44. 59; H, 2.49. Found C, 43.67; H, 1.89. %.

Synthesis of 3, 5-Bis (4-Fluorophenyl) Ioxazole (3):

Place 0.0125 moles of chalcone dibromide (2) and 1.75 g $NH_2OH.HCl$ in 2.5 ml H_2O in 5ml ethanol and heated for 15minute add a solution of 4.25 g KOH dissolved in 5 ml H_2O dropwise during 10 min. KCl and KBr salts were precipitated. Then cool the reaction mixture in ice and collect the solids, washed the solid with water to remove the salts and recrystallized the remaining solids from ethanol. M.p (C˚): 168-170, color: Grey, Yield: 67(%). IR: cm^{1}, 3030 (C-H) aromatic, 1590-1570 (C=C), 1685 (C=N), 1220 (C-F). ^{1}H-NMR: δ ppm 7.61 (s, 1H, CH), 7.39-7.99 (m, 8H, Ar-H). ^{13}C-NMR: δ ppm 97.13 (C-H), 115-128 (aromatic Carbon ring), 188 (C=O). Anal. Calcd for $C_{15}H_9F_2NO$: C, 70.04; H, 3.53; N, 5.45. Found C, 69.15; H, 2.87; N, 4.69 %

Synthesis of 3, 5-Bis (4-Fluoro Phenyl)-4-Halo Isoxazole (4, 5)

To a solution of the isoxazole (3) (0.0015 mole) in 5ml a glacial AcOH and added NBS or NIS (0.0017 mole) to the mixture and refluxed for 2 hrs. Excess water was added to give an appreciated, which is collected, washed with water, dried and recrystallized from EtOH. ***[4]:*** M. p (C˚): 171-173, color: Grey, Yield: 75(%). IR: cm^{1}, 3084 (C-H) aromatic, 1599-1499 (C=C), 1609 (C=N), 1154 (C-F), 732 (C-Br). ^{1}H-NMR: δ ppm 7.43-8.12 (m, 8H, Ar-H). ^{13}C-NMR: δ ppm 89.15 (C-Br), 122-123 (2C-Ph), 115.80-165.24 (aromatic carbon atoms). ^{19}F-NMR: δ ppm (-108.15-(-109.97)) (2C-F). Anal. Calcd for $C_{15}H_8F_2BrNO$: C, 53.60; H, 2.40; N, 4.17. Found C, 52.73; H, 1.72; N, 3.51. %. ***[5]:*** M.p (C˚): 156-158, color: White, Yield: 82 (%). IR: cm^{1}, 3147 (C-H) aromatic, 1597-1500 (C=C), 1690 (C=N), 1156 (C-F), 550 (C-I). ^{1}H-NMR: δ ppm 7.42-8.09 (m, 8H, Ar-H). Anal. Calcd for $C_{15}H_8IF_2NO$: C, 47.02; H, 2.10; N, 3.66. Found C, 46.17; H, 1.42; N, 2.97. %.

Synthesis of 3, 5-Bis (4-Fluoro Phenyl)-4-P-Aryl Isoxazole [6-9]

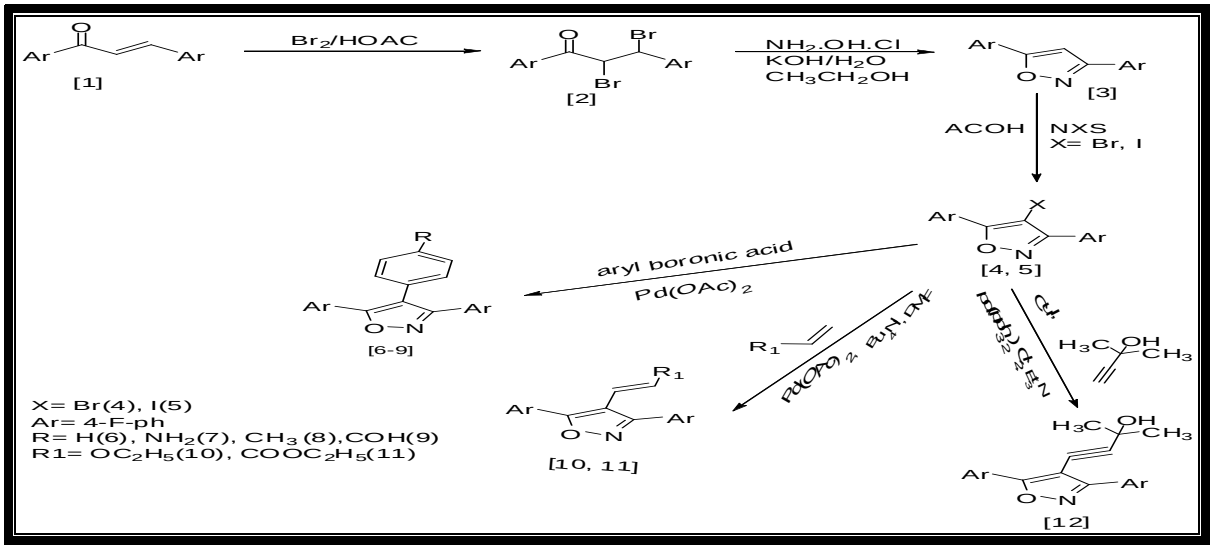
A mixture of Na_2CO_3 (0.212 g, 2 mole), Pd $(OAc)_2$ (0.002 g, 1mole), and poly ethylene glycol (PEG) 2000 (3.5 g) and 3ml water was heated to 50 C^{o} with stirring. Aryl halide [4, 5] (1 mole), and aryl boronic acid (1.5 mole) were added to the solution, and the reaction was carried out at 50 C^{o} for the indication time for 24 hrs. After the reaction solution was cooled to RT. The resulting suspension was extracted with diethyl ether (4 x 5 ml). The residue was dried using magnesium sulfate anhydrous. Further purification of the product was achieved based on the flash chromatography on a silica gel column. [***6]:*** M. p (C˚): 124-22, color: Beige, Yield: 54(%). IR: cm^{-1}, 2927-2877 (C-H) aromatic, 1608-1581 (C=C), 1624 (C=N), 1030 (C-F). ^{1}H-NMR: δ ppm 7.14-8.79 (m, 13H, Ar-H). ^{13}C-NMR: δ ppm 128-129 (aromatic carbon atoms). Anal. Calcd for $C_{21}H_{14}F_2N_2O$: C, 71.59; H, 3.72; N, 3.98. Found C, 70.72; H, 2.69; N, 3.12. %. [***7]:*** M.p (C˚): 95-97, color: Beige, Yield: 64 (%). IR: cm^{-1}, 3035-2985 (C-H) aromatic, 1595-1560 (C=C), 1634 (C=N), 3355-3311 (NH2), 1054 (C-F). ^{1}H-NMR: δ ppm 5.17 (s, 2H, NH_2), 7.43-8.27 (m, 13H, Ar-H. Anal. Calcd for $C_{21}H_{13}F_2NO$: C, 68.66; H, 3.84; N, 7.63. Found C, 67.93; H, 2.97; N, 6.89%. [***8]:*** M. p (C˚): 139-141, color: Beige, Yield: 52(%). IR: cm^{-1}, 3013 (C-H) aromatic, 1620-1582 (C=C), 1608 (C=N), 1054 (C-F). ^{1}H-NMR: δ ppm 2.41 (s, 3H, CH_3), 7.18-8.10 (m, 12H, Ar-H). ^{13}C-NMR: δ ppm 21.63 (CH_3), 128-129 (aromatic carbon atoms). Anal. Calcd for $C_{22}H_{15}F_2NO$: C, 72.13; H, 4.13; N, 3.82. Found C, 71.34; H, 3.51; N, 2.96%.[***9]:*** M.p (C˚): 151-153, color: Beige, Yield: 60 (%). IR: cm^{-1}, 2927 (C-H) aromatic, 1589-1446 (C=C), 1701 (C=O), 1624 (C=N), 1030 (C-F). Anal. Calcd for $C_{22}H_{13}F_2NO_2$: C, 69.47; H, 3.45; N, 3.68. Found C, 68.69; H, 2.86; N, 2.93%.

Synthesis of (E)-Ethyl 3-(3, 5-Bis (4-Fluorophenyl) Isoxazol-4-yl) Acrylate [10, 11]

A mixture of aryl halide [4,5] (1mol) and butyl acrylate (0.64 g, 5 mole) and Ethyl Vinyl Ether, palladium-complex, $Pd(OAc)_2$ (3mole), and tetrabutyl ammonium iodide (1.1 g, 3 mole) in 5ml DMF was allowed to reaction in a seal tube at 150 C^o for 48 hrs. The reaction mixture was heated with 5ml H_2O, followed using extracted with Et_2O (15 ml x3) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude material was purified by silica column chromatography using hexane-ethylacetate as an eluent to give the semi ppt. ***[10]:*** M.p (C˚): 155d, color: Yellow, Yield: 47 (%). IR: cm^1, 3193 (C-H) aromatic, 1608 (C=N), 1667 (C-O), 1590-1560 (C=C), 1093 (C-F). ^{1}H-NMR: δ ppm 7.14-8.79 (m, 13H, Ar-H). Anal. Calcd for $C_{20}H_{15}F_2NO_3$: C, 67.60; H, 4.25; N, 3.94. Found C, 66.78; H, 3.67; N, 3.05.%. [***11]:*** M.p (C˚): 143d, color: Yellow, Yield: 50 (%). IR: cm^1, 3067 (C-H) aromatic, 1654 (C=N), 1612-1563 (C=C), 1209 (C-F). Anal. Calcd for $C_{19}H_{15}F_2NO_2$: C, 69.72; H, 4.62; N, 4.28. Found C, 68.90; H, 3.85; N, 3.62%.

Synthesis of 4-(3, 5-Bis (4-Fluorophenyl) Isoxazol-4-yl)-2-Methylbut-3-yn-2-ol [12]

halo-oxazole [4, 5] (34.7 mole) and 2-methyl-3-bytyl-2-ol (4.37 g, 51.9 mole) were dissolved in 50 ml triethylamine. After the solution was degassed with N_2 for 30 min, Pd $(pph_3)_2Cl_2$ (0.03 g, 0.05 mole), and cuprous iodide (0.08 g, 0.4 mole) were added. As soon as a mixture was stirred under N_2 atmosphere, the solution turned turbid. Following reflux for 12 hrs, the mixture was cooled to RT. The solvent was removed using rotate evaporator. Then the residue was resolved in chloroform and dried with $MgSO_4$ overnight. The crude product was purified by column chromatography [silica gel] with eluent of dichloromethane / ethyl acetate 10:1 (v/v) to at afford a yellow gum, which is unstable for preservation. M.p (C˚): 153d, color: Yellow, Yield: 78(%). IR: cm^1, 3204 (O-H), 1651 (C=N), 2213 (C-C) triple bond, 1600-1514 (C=C), 1093 (C-F). ^{1}H-NMR: δ ppm 1.72 (S, 6H, $2CH_3$), 3.74 (S, 1H, OH), 7.23-8.08 (m, 8H, Ar-H), Anal. Calcd for $C_{20}H_{15}F_2NO_2$: C, 70.79; H, 4.46; N, 4.13. Found C, 69.91; H, 3.88; N, 3.45.%.



Scheme 3: The Synthetic Route for Novel Isoxazole Derivatives

CONCLUSIONS

In summary, we have synthesized new compounds using three major different reactions Suzuki, Hech, and Songashoria. We were synthesized (12) novel isoxazol derivatives including aryl, alkene and alkyne were substituted at 4-position of isoxazole ring.

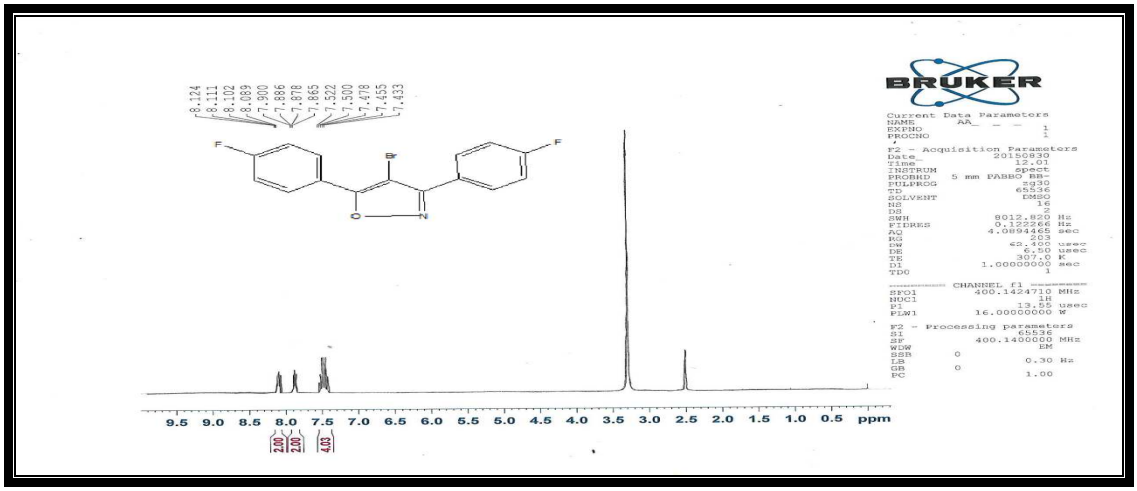


Figure 1: ^{1}H-NMR Spectrum of Compound (4)

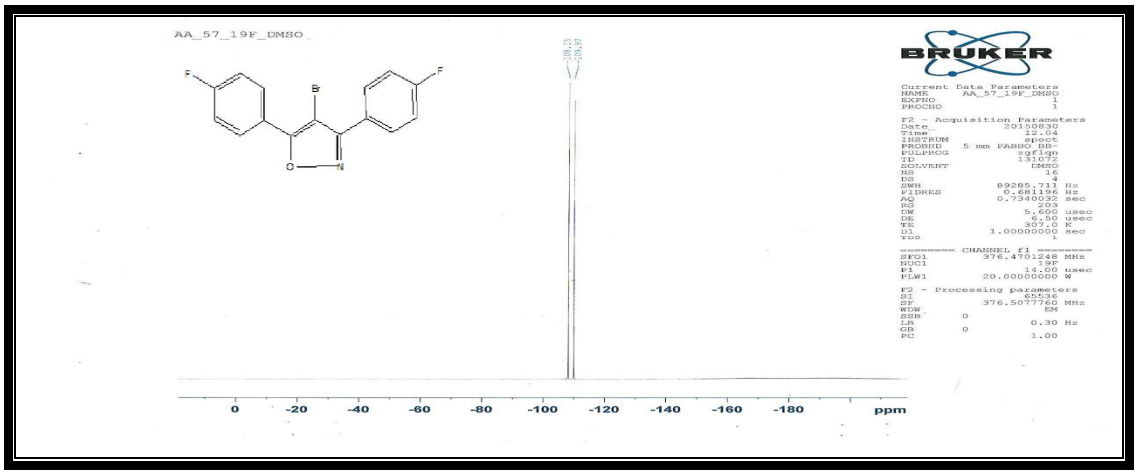


Figure 2: ^{19}F-NMR Spectrum of Compound (4)

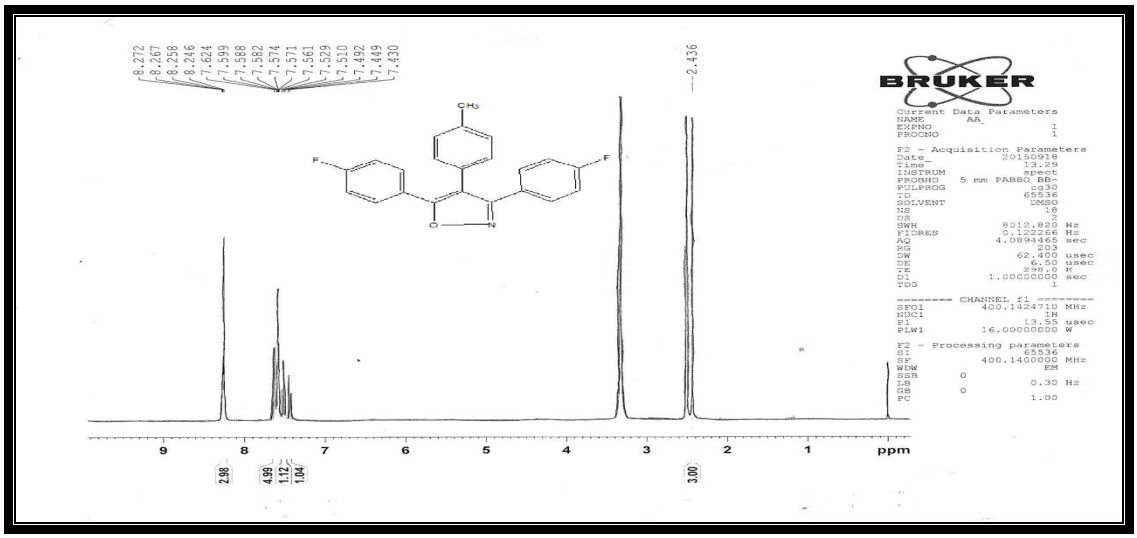


Figure 3: ^{1}H-NMR Spectrum of Compound (8)

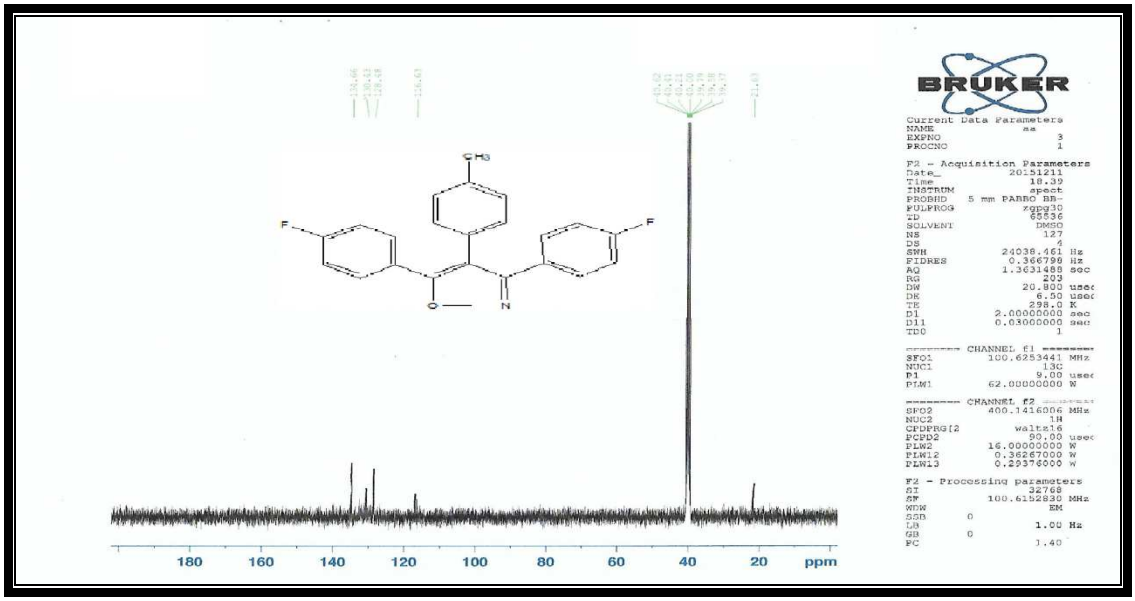


Figure 4: ^{13}C-NMR Spectrum of Compound (8)

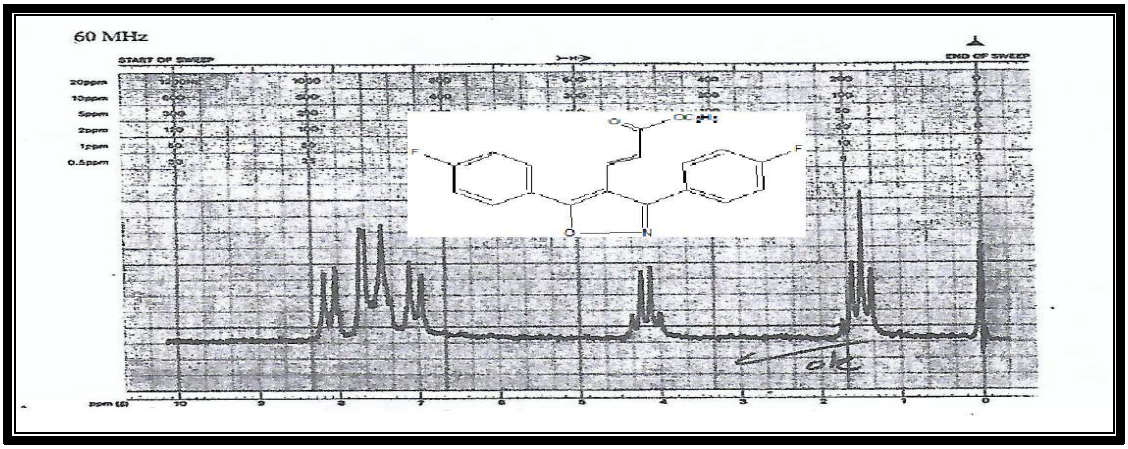


Figure 5: ^{1}H-NMR Spectrum of Compound (10)

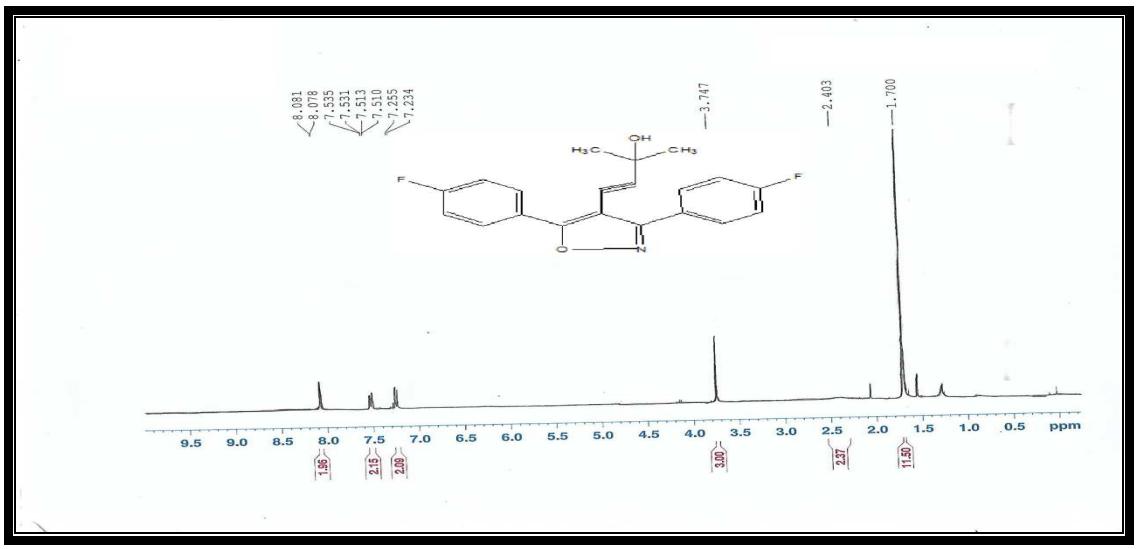


Figure 6: ^{1}H-NMR Spectrum of Compound (12)

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