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Research Article

SYNTHESIS AND CHARACTERIZATION OF SOME NEW 3',5-DIPHENYL -4,4',5,5'-TETRAHYDRO-3,5'-BIISOXAZOLE DERIVATIVES

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ABSTRACT

The synthesis and characterization of some novel isoxazoles derivatives have been presented. Isoxazoles have been prepared from 1,6-diphenylhexa-1,5-diene-3,4-dione by treating with hydroxylamine hydrochloride. The structure of isoxazoles has been characterized by spectral analysis by FT-IR, elemental analysis (C.H.N.) and ^{1}H NMR spectroscopy.

Keywords: Isoxazoline, Chalcone and Heterocyclic.

INTRODUCTION

Heterocyclic compounds are very widely distributed in nature, and are essential to life in various ways. Particularly these compounds are important because of the wide variety of physiological activities associated with this class of substances. Heterocyclic rings are present in several compounds, e. g, most of the members of vitamin B complex, antibiotics, chlorophyll, haemin, other plant pigments, amino acids and proteins, drugs, dye stuffs, enzymes, the genetic material DNA etc.

The paramount importance of heterocycles in nature product chemistry and pharmacology constantly drive the search for new methods for the construction of heterocyclic unit viz., isoxazoles and pyrazoles. These isoxazoles and pyrazoles were prepared from chalcones which are important intermediate products and they also possess biological and pharmacological activities[1].

Isoxazoles possess interesting medicinal[2] properties and have some industrial utility[3]. Many biologically active isoxazoles and reduced isoxazole derivatives have been reported, viz., the naturally occurring antituberculosis, antibiotic cycloserine, the mono amine oxidase inhibitor: isocarboxazid, useful in psychotherapy and Isoxazole steroids show anabolic activity, eg., Denazole[4]. The CNS active isoxazoles, ibotenic acid, muscimol and muscazone are isolated from amanita muscaria and other amanita species. Isoxazole derivatives were used as inhibitors for ulcers[5], lipoxygenase[6], acetyl choline esterase[7]. 3-Substituted 5-methylthio isoxazoles were found to exhibit anthelmintic activity[8]. Spiroisoxazolines[9] and benzofuroisoxazoles[10] were used as anti-convergents. 5-Amino-3-methyl-4-ureidoisoxazoles were found to exhibit anti-leukemic activity[11]. Some new 2-isoxazole derivatives prepared from a,ß-dibromochalcones showed mild antibacterial activity[12]. A group of 4,5-diphenyl isoxazoles, 3,4diphenyl-5-trifluoro methyl isoxazoles and 4,5-diphenyl-3-methyl sulfonoamido isoxazole possessing a variety of substitutions (H, F, MeS, MeSO, MeSO2) at the para position of one of the phenyl rings were used as analgesic and selective COX-2 inhibitory, and anti-inflammatory agents[13]. Isoxazolyl naphthoquinones act as potential trypanocidal and antibacterial agents[14].

Experimental

General

Melting points were uncorrected. FT.IR-8400,SHIMADZU. NMR spectra were acquired with a Bruker Ultra Shield (^{1}H : 300 MHz) (University of AL-al-Bayt,Jordan). The chemical shifts were referenced to tetra methyl silane (TMS) as an internal standard. The elemental analysis were performed by using Euro Vector EA3000A (University of AL-al-Bayt,Jordan).

Synthesis of isoxazoline derivatives (2a-e)
General procedure
A mixture of Chalcone (**1a–e**) (which was prepared as mentioned in the literature)[15] (0.02mol), hydroxylamine hydrochloride (0.02 mol) were dissolved in ethanolic sodium hydroxide (10ml) was reflux overnight. The precipitate obtained was filtered, washed and recrystallized from ethanol. The progress of the reaction was monitored by TLC (ethyl acetate/hexane, 8:2). The EtOH was removed under reduced pressure and the residue was recrystalized from EtOH to afford the pure products (**2a–e**).

3',5-diphenyl-4,4',5,5'-tetrahydro-3,5'-biisoxazole (2a)
was prepared from the reaction of 1,6-diphenylhexa-1,5-diene-3,4-dione (1a) with hydroxylamine hydrochloride and gave a 71% yield with a m.p. (200-201)^{o}c. The CHN analysis for $C_{18}H_{16}N_2O_2$; C, 73.95; H, 5.52; N, 9.58; Found C 73.92; H 5.50 ; N 9.57, FT-IR spectra (KBr pellet) υ(cm^{-1}) 3020 (C–H stretching of aromatic ring), 2880 (C–H stretching of aliphatic), 1614 (C=N stretching of isoxazoline ring), 1595 (C=C stretching of aromatic ring), 1219 (C–N stretching of isoxazoline ring), 1119 (N–O stretching of isoxazoline ring), $\delta_H(CDCl_3)$ (7.271-7.417) ppm (10H,m,1,2,3); (3.927-3.937) ppm (2H,t,4) ; (2.625-2.725) ppm (4H,d,6,6/)

3',5-dip-tolyl-4,4',5,5'-tetrahydro-3,5'-biisoxazole (2b)
was prepared from the reaction of 1,6-dip-tolylhexa-1,5-diene-3,4-dione (1b) with hydroxylamine hydrochloride and gave a 74% yield with a m.p. (202-204)^{o}c. The CHN analysis for $C_{20}H_{20}N_2O_2$; C, 74.98; H, 6.29; N, 8.74; Found C 74.97; H 6.27; N 8.47, FT-IR spectra (KBr pellet) υ(cm^{-1}) 3022 (C–H stretching of aromatic ring), 2883 (C–H stretching of aliphatic), 1619 (C=N stretching of isoxazoline ring), 1594 (C=C stretching of aromatic ring), 1216 (C–N stretching of isoxazoline ring), 1120 (N–O stretching of isoxazoline ring); $\delta_H(CDCl_3)$ (7.000-7.012) ppm (4H,t,2); (7.100-7.180) ppm (4H,d,3); (3.920-3.930) ppm (2H,t,4) ; (2.630-2.740) ppm (4H,d,6,6/) ; 2.340 ppm (6H,s,1)

5,'3 -bis(4-methoxyphenyl)-4,4',5,5'-tetrahydro-3,5'-biisoxazole (2C)
was prepared from the reaction of 1,6-bis(4-methoxyphenyl)hexa-1,5-diene-3,4-dione (1c) with hydroxylamine hydrochloride and gave a 70% yield with a m.p. (195-196)^{o}c. The CHN analysis for $C_{20}H_{20}N_2O_4$; C, 68.17; H, 5.72; N, 7.95; Found C 68.15; H 5.71; N 7.93, FT-IR spectra (KBr pellet) υ(cm^{-1}) 3020 (C–H stretching of aromatic ring), 2880 (C–H stretching of aliphatic), 1620 (C=N stretching of isoxazoline ring), 1590 (C=C stretching of aromatic ring), 1210 (C–N stretching of isoxazoline ring), 1118 (N–O stretching of isoxazoline ring); $\delta_H(CDCl_3)$ (6.940-6.950) ppm (4H,t,2); (7.180-7.190) ppm (4H,d,3); (3.910-3.920) ppm (2H,t,4) ; (2.626-2.726) ppm (4H,d,6,6/) ; 3.700 ppm (6H,s,1)

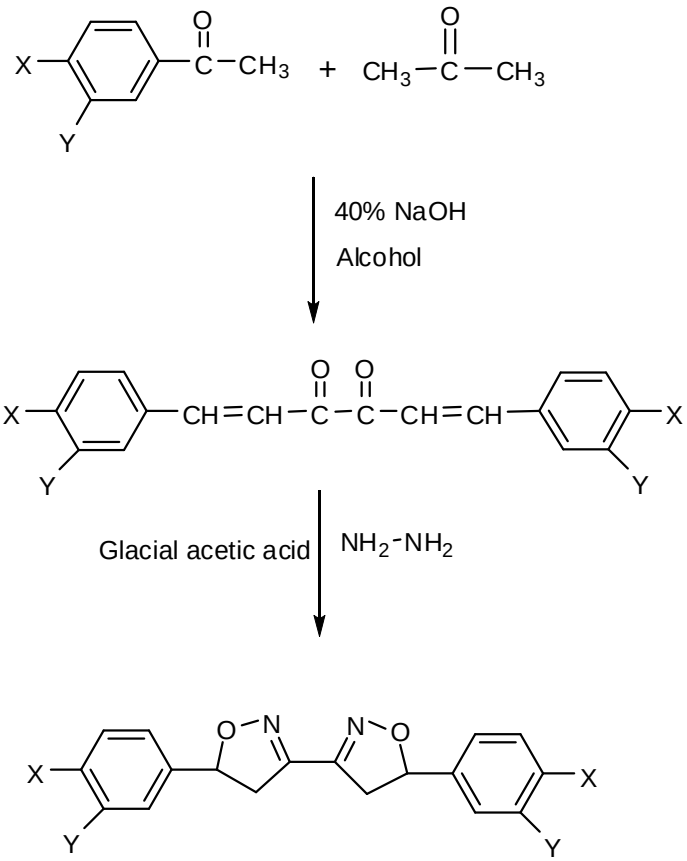
3',5-bis(4-chlorophenyl)-4,4',5,5'-tetrahydro-3,5'-biisoxazole (2d)
Was prepared from the reaction of 1,6-bis(4-chlorophenyl)hexa-1,5-diene-3,4-dione (1d) with hydroxylamine hydrochloride and gave a 78% yield with a m.p. (203-205)^{o}c. The CHN analysis for $C_{18}H_{14}C_{l2}N_2O_2$; C, 59.85; H, 3.91; N, 7.76; Found C 59.82; H 3.90; N 7.74, FT-IR spectra (KBr pellet) υ(cm^{-1}) 3024 (C–H stretching of aromatic ring), 2885 (C–H stretching of aliphatic), 1622 (C=N stretching of isoxazoline ring), 1595 (C=C stretching of aromatic ring), 1214(C–N stretching of isoxazoline ring), 1122 (N–O stretching of isoxazoline ring); $\delta_H(CDCl_3)$ (7.440-7.480) ppm (8H,m,2,3); (3.940-3.950) ppm (2H,t,4) ; (2.629-2.739) ppm (4H,d,6,6/) .

4,4'-(4,4',5,5'-tetrahydro-3,5'-biisoxazole-3',5-diyl)bis(2-methoxyphenol) (2e)
Was prepared from the reaction of 1,6-bis(4-hydroxy-3-methoxyphenyl)hexa-1,5-diene-3,4-dione (1e) with hydroxylamine hydrochloride and gave a 69% yield with a m.p. (205-207)^{o}c. The CHN analysis for $C_{20}H_{20}N_2O_6$; C, 62.49; H, 5.24; N, 7.29; Found C 62.47; H 5.23; N 7.29, FT-IR spectra (KBr pellet) υ(cm^{-1}) 3250 (OH stretching of phenol ring), 3024 (C–H stretching of aromatic ring), 2885 (C–H stretching of aliphatic), 1622 (C=N stretching of isoxazoline ring), 1595 (C=C stretching of aromatic ring), 1214(C–N stretching of isoxazoline ring), 1120 (N–O stretching of isoxazoline ring); $\delta_H(CDCl_3)$ 9.711 ppm (1H,s,1 (OH)), (6.680-6.900) ppm (5H,m,2,3); (3.900-3.910) ppm (2H,t,4) ; (2.620-2.730) ppm (4H,d,6,6/) ; 3.800 ppm (6H,s,2/)

RESULTS AND DISCUSSION
Treatment of chalcones derivatives **(1a-e)** with hydroxylamine hydrochloride in boiling ethanol gave isoxazoline derivatives compounds, after purification by recrystallization from ethanol, pure isoxazoline derivatives compounds as shown in (scheme 1) in (69-78)% yield. The structures of these products were established from their elemental analysis, FT-IR,C.H.N and ^{1}H NMR spectra. The FT-IR spectra of isoxazoline compounds were characterized by the disappearance of the absorption band that

was attributed to the (C=O) stretching which appeared at (1672-1710) cm^{-1}. These fact confirmed the correct expected chemical structure of these compounds. All the IR spectra of isoxazoline derivatives showed a peak at (1614-1625) cm^{-1} which related to (C=N) stretching of isoxazoline ring , a peak at (1210-1219) cm^{-1} which appeared due to (C-N) stretching of isoxazoline ring, peak at (1118-1122) cm^{-1} which appeared due to (N-O) stretching of isoxazoline ring and a peak at (1590-1597) cm^{-1} which appeared due to (C=C stretching of aromatic ring). While, the C-H stretching aromatic rings showed a peak within the range (3020-3024) cm^{-1} and the C-H stretching aliphatic showed a peak within the range (2880-2885) cm^{-1}. The OH stretching of phenolic ring showed a peak within the range 3250 cm^{-1}.

All the ^1H NMR spectra of isoxazoline ring were characterized[16-19] by the presence showed triplet signals within the range (3.900-3.950) ppm which appeared to proton in (4) position because interaction with two protons in (6 and 6\) position , while the two protons in (6 and 6\) position showed doublet signals within the range (2.620-2.740) ppm because interaction with protons in (4) position. The protons of aromatic rings in compound (2a) and (2d) showed multiplet signals within the range (6.680-7.480) ppm which appeared to protons in (1,2 and 3). While the compounds (2b,2c) showed doublet signals within the range (6.940-7.012) ppm which appeared to the two protons in (2 and 3) positions.. The OCH_3 protons showed singlet signal for six protons at (3.700-3.800) ppm. The OH protons showed singlet signal for two protons in the region δ= 9.711 ppm.While the CH_3 protons showed singlet signal for six protons at 2.340 ppm.



Scheme (1)

X	Y	Compound Chalcone	Compound Pyrazoline
H	H	1a	2a
CH_3	H	1b	2b
OCH_3	H	1c	2c
Cl	H	1d	2d
OH	OCH_3	1e	2e

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