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Synthesis and Characterization of Some New Schiff Base Containing 4, 5-Dihydroisoxazole Moieties

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Abstract. A series of Schiff bases combined with 4, 5-dihydroisoxazole moieties as derivatives of chalcone were synthesized. Schiff base compounds containing chalcone group were prepared by the treatment of one mole of dicarbonyl compound, such as benzil, with one mole of different amine compounds and the products were reacted with acetone. The results were reacted with hydroxylamine hydrochloride in ethanol and glacial acetic acid as a catalyst for synthesis various derivatives of 4, 5-dihydroisoxazole moieties that combined with Schiff bases. The structures of the new synthesized compounds, Schiff bases combined with 4, 5-dihydroisoxazole moieties, have been established on the basis of their spectral data (FTIR, ¹H NMR, ¹³CNMR and MASS).

INTRODUCTION

Considerable interest in the synthesis of chalcone derivatives exists due to their potential for practical applications. Functionalized α , β -unsaturated keto group in chalcones are present in many pharmacologically active substances. [1] The presence of reactive unsaturated group in chalcones is found to be responsible for their biological activity. In the present work chalcones have been prepared by condensing one mole of acetone with one mole of dicarbonyl aromatic ketone. Recently, it was reported that chalcones exhibit strong scavenging activity. Schiff base extensive interest among scientists worldwide because of their versatility and ease of preparation [2] and it serves as a backbone for the synthesis of various heterocyclic compounds and show antioxidant activity and strongly inhibit lipopolysaccharide. [3] They have been utilized as a base molecules in the preparation of a number of industrial and biologically active compounds like formazans, 4-thiazolidinines, benzoxazines, ring closure, cycloaddition, and replacement reactions. [4] Schiff base compounds found application in the synthesis of organic dyes. The interest in heterocyclic compounds has been growing particularly five Member ring compounds have occupied the first place among various classes of organic compounds for their diverse biological activities. [5] These compounds possess one or the other chemotherapeutic or pharmacological activities. The oligomers and polymers of heterocyclic compounds have been widely used in photovoltaic cells because of their chemical and environmental stability and their electronic tenability [6]. Isoxazole compounds occupy a unique place in the realm of natural and synthetic organic chemistry. [7] Isoxazole compounds have found wide applications in the fields of pharmacological activity. [8] They are very widely found in bioorganic and medicinal chemistry application in drug discovery such as antihistaminic, anticancer, antiviral, antiHIV, antifungal, antibacterial, anti-inflammatory, anticonvulsant and anti-tuberculo-static. [9] Isoxazole compounds as a prevent cancer; it has been studied for its ability to improve the immune system functions and as a scavenger of free radicals [10] and they are able to reduce oxidative stress which is the most likely mechanism mediating the protective effects against cancer development. [11], [12] in the present work, Based on the above observations, we report our results for combining these two important class of compounds (Schiff base and isoxazole) in one compound and synthesis some new compounds of Schiff bases combined with 4, 5-dihydroisoxazole as derivatives of chalcones.

MATERIALS AND METHODS

The synthesized compounds were prepared according to literature procedures. All chemicals were obtained from standard commercial sources. The chemicals used (supplier and purity): Sigma-Aldrich (benzil 98 %, glacial acetic acid 99%, benzylamine 97% and 4-chlorobenzylamine 97%, 1-naphthylamine 99%, 4-aminobenzoic acid 99%) and Merck (sodium hydroxide 97%, acetone 99%, ethanol 99% and aniline 99.5%).

Schiff base compounds containing chalcone were prepared by the condensation reaction of one mole of benzil with one mole of different substituted amine and the products were reacted with acetone. 4, 5-Dihydroisoxazol compounds were synthesized by the reaction of chalcone with hydroxylamine hydrochloride in ethanol and glacial acetic acid as a catalyst.

FT-IR spectra were recorded using a Bruker spectrometer. $[1]H$ and $[13] C$ NMR spectra were recorded in DMSO and δ units downfield from internal reference Me₄Si. Using a 300 MHz Bruker NMR spectrometer. The mass spectra were recorded on a Shimadzu QP GC-MS instrument. Melting points were measured with an Electro thermal IA 9200 apparatus.

The General Method to Prepare Schiff Bases [13]

A solution of benzil, (0.028 moles) in absolute ethanol 30 ml was added to a solution of amine, (0.028 moles) in absolute ethanol 30 ml placed in a 250 ml one-necked round bottomed flask. The reaction mixture was heated to 78 ° C and refluxed in the dark (4-6) hr. The progress of the reaction was monitored by TLC. The reaction mixture was cooled and the precipitate was filtered and then recrystallized from absolute ethanol.

The General Method to Prepare Chalcone [14]

A solution of (5 ml) of benzaldehyde and (2 ml) of acetone, placed in a 250 ml one-necked round bottomed flask. The reaction mixture was stirred and then a solution of (5 g) of sodium hydroxide in (50 ml) of water and (40 ml) of ethanol was added at room temperature. The reaction mixture was stirred vigorously until the mixture is so thick that stirring is no longer effective (0.5 hr.). The progress of the reaction was monitored by TLC. The product was filtered and washed with cold water and then recrystallized from 10 ml ethanol.

The General Method to Synthesis 4, 5-Dihydroisoxazole [15]

A solution of hydroxylamine hydrochloride (2.0 mmol) and glacial acetic acid (2.5 ml) was added to a stirred solution of chalcone (1.0 mmol) in (10 ml) ethanol at room temperature. The reaction mixture was heated to 78 ° C and refluxed for (18-24) hr. The progress of the reaction was monitored by TLC. The ethanol was removed under reduced pressure and the result was recrystallized from ethanol. The equations of reaction explain in (Fig. 1). All the results were in agreement with the expected structure. The physical properties of new Schiff base containing isoxazole are represented in table (1).

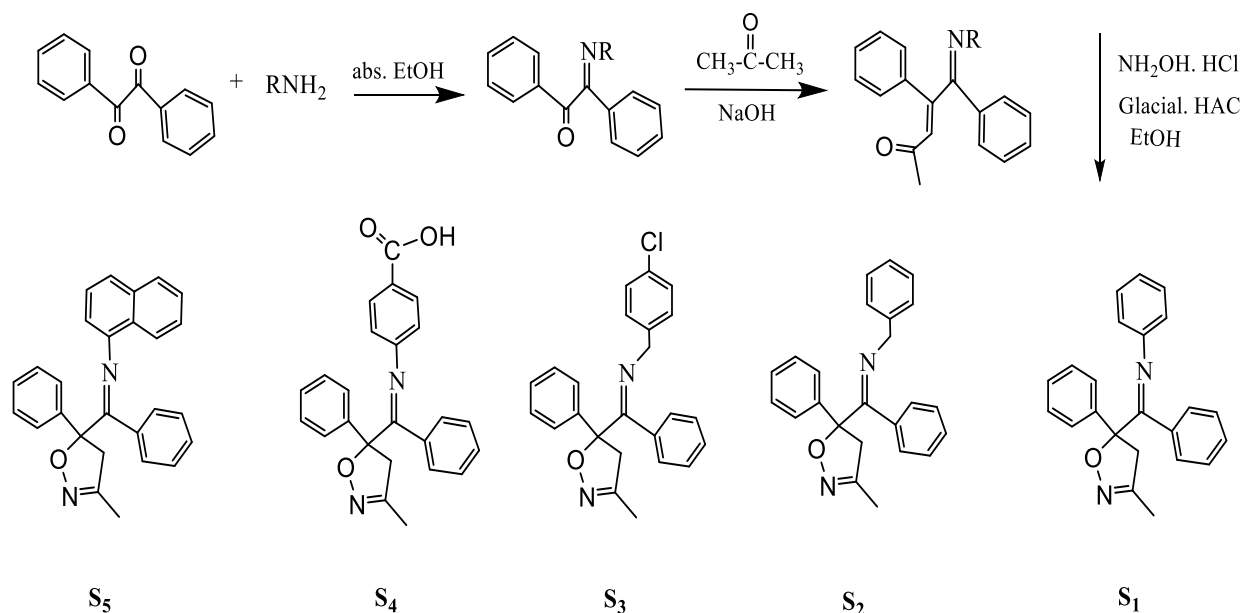


Figure 1. The equations of synthesis Schiff Base Containing 4, 5-Dihydroisoxazole.

TABLE 1. Physical properties of new Schiff base containing 4, 5-Dihydroisoxazole.

Comp	M. p °C	Time of reaction	Yield (%)	Solution of TLC	Rf
S ₁	134-136	24	76	Ethyl acetate + Ethanol	0.6
S ₂	156-157	20	73	Ethyl acetate + Ethanol	0.5
S ₃	130-131	20	80	Ethyl acetate + Ethanol	0.5
S ₄	245-246	21	71	Ethyl acetate + Ethanol	0.8
S ₅	211-212	81	70	Ethyl acetate + Ethanol	0.6

(S₁) 1-(3-methyl-5-phenyl-4,5-dihydroisoxazol-5-yl)-N,1-diphenylmethanimine

Orange crystals; yields: 76%; m.p. 134-136 °C; IR (ν cm⁻¹): 1609 (ν C=N), 1284 (ν C-N), 1189 (ν N-O), 1568 (ν C=C), 3110 (ν CH aromatic), 2895-2877 (ν CH aliphatic), 1104 (ν C-O); ¹H NMR (DMSO, 300 MHz; δ ppm) δ : 7.70 (m, 5H, ph), 6.82 (m, 5H, ph), 6.52 (m, 5H, ph), 2.52 (s 2H, CH₂), 1.61 (s, CH₃); ¹³C NMR (DMSO, 300 MHz; δ ppm): 55.65, 63.22, 112.97, 121.07, 123.11, 125.26, 127.05, 128.75, 129.07, 130.45, 130.90, 131.99, 132.73, 133.65, 139.00, 141.36, 161.54; MS: m/z: 340 (M⁺).

(S₂) N-benzyl-1-(3-methyl-5-phenyl-4, 5-dihydroisoxazol-5-yl)-1-phenylmethanimine

Yellow crystals; yields: 73%; m.p. 156-157 °C; IR (ν cm⁻¹): 1611 (ν C=N), 1220 (ν C-N), 1153 (ν N-O), 1587 (ν C=C), 3100 (ν CH aromatic), 2891-2887 (ν CH aliphatic), 1107 (ν C-O); ¹H NMR (DMSO, 300 MHz; δ ppm) δ : 7.02 (m, 5H, ph), 6.86 (m, 5H, ph), 6.63 (m, 5H, ph), 2.32 (s 2H, CH₂), 2.53 (s 2H, CH₂), 1.42 (s, CH₃); ¹³C NMR (DMSO, 300 MHz; δ ppm): 51.75, 59.75, 111.53, 116.82, 117.35, 120.25, 121.52, 122.73, 124.63, 126.46, 127.84, 129.94, 130.57, 131.54, 132.58, 133.27, 142.08, 159.05; MS: m/z: 354 (M⁺).

(S₃) N-(4-chlorobenzyl)-1-(3-methyl-5-phenyl-4,5-dihydroisoxazol-5-yl)-1-phenylmethanimine

Orange crystals; yields: 80 %; m.p. 130-131 °C; IR (ν cm⁻¹): 1599 (ν C=N), 1254 (C-N), 1201 (ν N-O), 1551 (ν C=C), 3113 (ν CH aromatic), 2896-2870 (ν CH aliphatic), 1098 (C-O), 798 (C-Cl); ¹H NMR (DMSO, 300 MHz; δ ppm) δ : 7.52 (m, 4H, ph), 7.22 (m, 5H, ph), 7.00 (m, 5H, ph), 3.22 (s 2H, CH₂), 2.72 (s 2H, CH₂), 1.64 (s, CH₃); ¹³C

NMR (DMSO, 300 MHz; δ ppm): 57.85, 61.96, 111.75, 115.56, 117.43, 118.46, 120.48, 121.57, 122.46, 125.35, 127.45, 129.99, 130.85, 132.45, 134.35, 135.54, 147.54, 148.54; MS: m/z: 388 (M^+).

(S₄)4-(((3-methyl-5-phenyl-4,5-dihydroisoxazol-5-yl)(phenyl)methylene)amino)benzoic acid

Orange crystals; yields: 71 %; m.p. 245-246 °C; IR (ν cm^{-1}): 1604 (ν C=N), 1263 (ν C-N), 1151 (ν N-O), 1574 (ν C=C), 3120 (ν CH aromatic), 2874-2860 (ν CH aliphatic), 1164 (ν C-O), 1702 (ν C=O), 3312 (ν OH); ¹H NMR (DMSO, 300 MHz; δ ppm) δ : 7.45 (m,4H, ph), 7.12 (m,5H, ph), 6.90 (m,5H, ph), 2.01 (s 2H, CH₂), 1.76 (s, CH₃), 10.01 (s, OH); ¹³C NMR (DMSO, 300 MHz; δ ppm): 68.56, 81.76, 113.45, 114.56, 117.40, 117.99, 120.45, 121.34, 122.44, 123.57, 126.56, 128.66, 130.44, 131.09, 133.35, 145.46, 167.01, 168.67; MS: m/z: 384 (M^+).

(S₅)1-(3-methyl-5-phenyl-4,5-dihydroisoxazol-5-yl)-N-(naphthalene-1-yl)-1-phenylmethanimine

Brown crystals; yields: 70 %; m.p. 211-212 °C; IR (ν cm^{-1}): 1600 (ν C=N), 1232 (ν C-N), 1170 (ν N-O), 1569 (ν C=C), 3110 (ν CH aromatic), 2896-2877 (ν CH aliphatic), 1109 (ν C-O); ¹H NMR (DMSO, 300 MHz; δ ppm) δ : 7.79(m,5H, ph), 7.70(m,5H, ph), 7.62(m,7H, ph), 2.04 (s 2H, CH₂), 1.36 (s, CH₃); ¹³C NMR (DMSO, 300 MHz; δ ppm): 63.73, 72.89, 110.54, 112.84, 113.95, 114.86, 116.93, 118.56, 119.65, 120.34, 121.53, 121.99, 122.04, 122.94, 124.96, 126.34, 127.07, 130.45, 132.45, 133.34, 146.07, 166.55, 169.23; MS: m/z: 390 (M^+).

RESULTS AND DISCUSSION

The reaction of several schiff base compounds containing chalcone with hydroxylamine hydrochloride gave the corresponding Schiff base containing 4, 5-dihydroisoxazole derivatives in good yields (Experimental section). All results compounds are yellow to orange crystalline solids with sharp melting point which are soluble in common organic solvents. All the IR spectra of new Schiff base containing isoxazole moieties showed the disappearance peaks due to the stretching vibration of (C=O) of carbonyl band in the region (1700-1670) cm^{-1} of benzil compound. The spectra showed the appearance peaks due to the stretching vibration of (C=N) and (N-O) bands in the region (1599-1611) and (1151-1201) cm^{-1} , respectively. The spectra showed peaks due to the stretching vibration of (C-H) aromatic and (C-H) aliphatic bands within the range (3100-3120) and (2874-2887) cm^{-1} . The spectrum of synthesized compound (S₃) showed a peak due to the stretching vibration of (C-Cl) group in the region (798) cm^{-1} , while the spectrum of synthesized compound (S₄) showed peaks due to the stretching vibration of (C=O) and (OH) groups in the region (1702) and (3312) cm^{-1} , respectively. All the ¹H NMR spectra of new synthesized compounds were showed multiples signals due to the protons of aromatic rings in the region (6.52-7.79) ppm and showed a singlet signal due to the protons of (CH₃) group in the region (1.36-1.76) ppm. The spectra showed a singlet signal due to the protons of CH₂ group of isooxazole ring in the region (2.01-3.22) ppm. The spectra of synthesized compound (S₂) and (S₃) showed a singlet signal due to the protons of (CH₂) group of benzyl group in the region (2.53-2.72) ppm, while the spectrum of synthesized compound (S₄) showed a singlet signal due to the proton of (OH) group in the region (10.01) ppm. All the ¹³C NMR spectra of new synthesized compounds were in agreement with the suggested structures. MASS spectra gave the molecular ion and other fragments which indicated the structure of synthesized compounds.

CONCLUSIONS

A result of present study demonstrate that, the new classes of Schiff base combined with 4, 5-dihydroisoxazole moieties compounds were synthesized and all these new compounds are stable toward moisture and light. The new synthesized compounds were characterized by IR, NMR and MASS spectroscopic data.

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