RESEARCH ARTICLE

Synthesis and Characterization of Few New Substituted 1,3,4-Oxadiazoles 1,2,4-Triazoles and Schiff Bases *via* Chalcone Compounds

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ABSTRACT

The synthesis of substituted 1,3,4-oxadiazol, 1,2,4-triazol and Schiff base from chalcones has been achieved. Mercapto acetic acid was reacted with the chalcone compound (1) to form carboxylic acid (2). Esterification of compound (2) has been accomplished through acidic conditions to give compound (3). The reaction of the ester (3) with $N_2H_4.H_2O$ gave the acid hydrazide compound (4). Stirring of (4) with CS_2 and KOH form compound (5), while refluxing of the same compound (4) in similar conditions gave oxadiazole (6). Substituted oxadiazole (7) was obtained through the reaction of (6) with benzyl bromide. Cyclization of compound (5) produced 1,2,4-triazole (8), which was treated with methyl iodide to give compound (9). Schiff bases were obtained by treatment of (4) with substituted acetophenone. The structure for the synthesized compounds has been proven by physical and spectral Infrared and Proton nuclear magnetic resonance (IR and ^{1}H-NMR) data.

Keywords: 1,2,4-Triazoles, 1,3,4-Oxadiazoles, Chalcones, Schiff bases.

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INTRODUCTION

The heterocyclic compounds and their derivatives are cyclic compounds with at least two different elements as ring member atoms.[1] It is also considered an important class in organic chemistry.[2] Heterocyclic compounds involve derivatives of 1,3,4–oxadiazole, 1,2,4–triazole and Schiff bases [3] have been widely reported and still playing a major role in the pharmaceutical chemistry.[4] They also have a wide range of medical, biological, and pharmacological activities.[5] Triazole is five-membered ring heterocyclic compound containing three nitrogen atoms.[6] Nowadays, the importance of triazoles and its derivatives comes from using this moiety in the design and synthesis of new compounds.[7] They are also considered an important molecule in bioactive synthesis linked to many biological activities.[8] Oxadiazol is a five-membered ring heterocyclic compound consisting of three atoms (two atoms of nitrogen with one atom of oxygen).[9] 1,3,4-Oxadiazole and its derivatives have great biological properties[10] with many examples in the literature such as antiviral, antifungal, antimicrobial, anti-inflammatory and anticancer activities.[11-15] Moreover, many studies showed that the existence of more than two heterocyclic units may lead to an increase the antimicrobial activity significantly.[16] Schiff bases are compounds carrying azomethine functional group[17] (C=N), Schiff bases obtained from complexes derived heterocycles have a great importance in the field of pharmaceutical industries due to versatile uses in synthetic intermediates and the wide range of biological properties.[18] For example, antifungal,[19] antibacterial,[20] analgesic and anti-inflammatory,[21] anticonvulsant,[22] anticancer [23] and antituberculosis activities.[24]

RESULTS AND DISCUSSION

The target compounds were synthesized, and the structure of the newly prepared compounds has been proven by infrared and Nuclear magnetic resonance (NMR) spectroscopy. The starting compound (1) was prepared according to the literature.[25] Compound (2) has been obtained from the reaction between chalcone compound (1) with 2-mercaptoacetic acid and ethanol with good yield 81%. The structure of compound (2) was confirmed by Proton nuclear magnetic resonance (^{1}H-NMR) which showed the disappearance the protons of the C=C double bond signal at δ 8.13 and δ 7.74 ppm related to the chalcone compound. Further, the IR spectrum has been shown a broad band at 3420 cm^{-1} belongs to the stretching of the hydroxyl group of the carboxylic acid which confirms the

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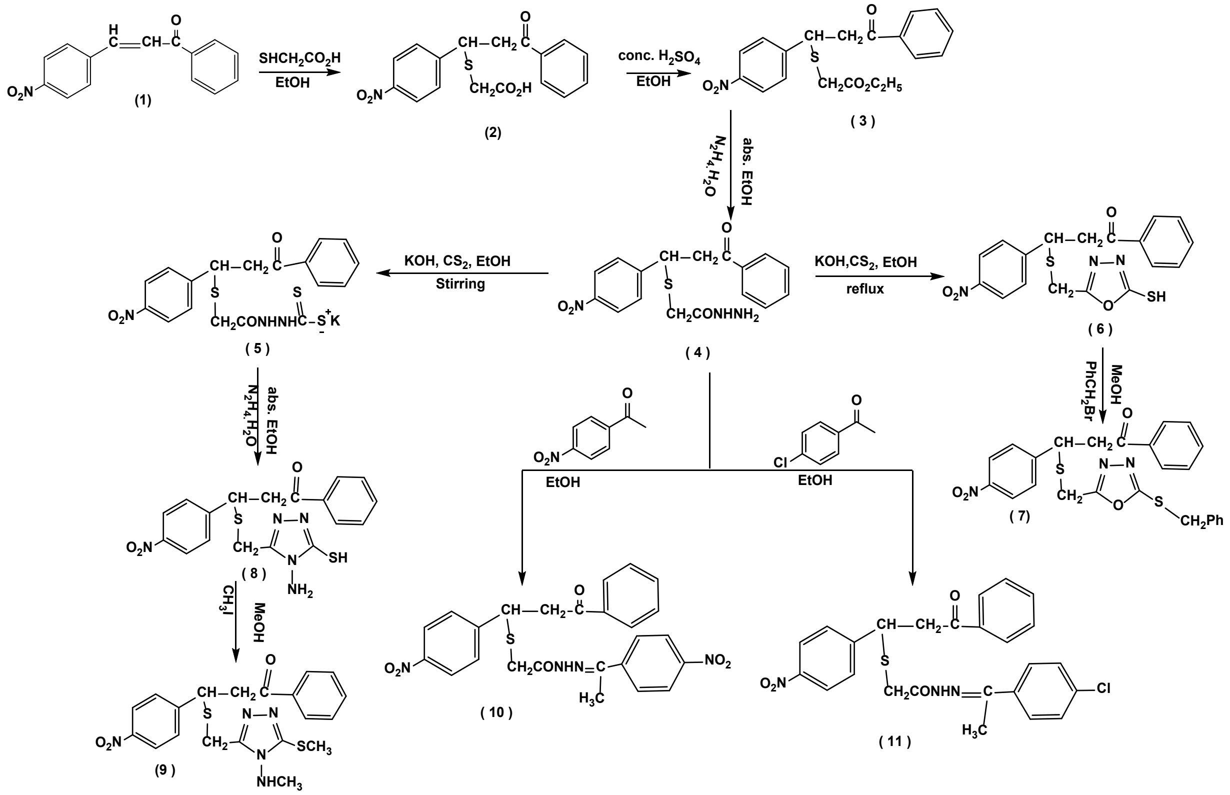
formation of the free acid. The esterification of compound (2) was carried out successfully using absolute ethanol in conc. H_2SO_4 to give compound (3). The structure was again confirmed by ^{1}H-NMR spectroscopy which showed triplet and quartet signals at δ 1.38 and δ 4.18 ppm, respectively. Acid hydrazide (4) resulted from the treatment of ethyl ester (3) with $N_2H_4.H_2O$ in absolute ethanol. The ^{1}H-NMR spectroscopy proved the formation of the desired product, which revealed the disappearance of the ester protons and the appearance of amino protons as a singlet at δ 6.31 ppm. In the contrary, the substituted thiosemicarbazide compound (5) was successfully synthesized by the conversion of the acid hydrazide compound (4) by treatment with CS_2 and ethanol in the presence of KOH. The ^{1}H-NMR showed the disappearance of the amino group protons, and the IR spectrum showed a band at 1188 cm^{-1} related to (C=S) group. The same way mentioned above for synthesizing compound (5) has been followed with slight modification for synthesizing the oxadiazole compound (6) by refluxing under alkaline medium. The reaction mechanism can be illustrated by nucleophilic attack of the nitrogen atom of the acid hydrazide at the carbon atom of CS_2 to form the salt which undergoes intra-nucleophilic attack of the C=O oxygen on the carbon atom of C=S group followed by elimination of hydrogen sulfide. The ^{1}H-NMR gave a singlet at δ 2.0 ppm corresponding to the thiol proton, while IR showed a band at 1645 cm^{-1} for (C=N), 1173 cm^{-1} for (C=S) and 1070 cm^{-1} for (C-O-C) group. This established the first evidence for the successful synthesis of the targeted compound. Thioether compound (7) was synthesized by treating of compound (6) with benzyl bromide in 20% solution of sodium hydroxide in methanol, again the structure was proven by ^{1}H-NMR which showed a signal δ 4.30 ppm belongs to the benzylic protons. Substituted 1,2,4-triazole compound (8) was obtained via the cyclization of compound (5) in the presence of hydrazine hydrate and absolute ethanol. The IR spectrum of product (8) offered 1581 cm^{-1} (C=N) and 1198 cm^{-1} (C=S), while the ^{1}H-NMR showed signals belong to the protons of amino and thiol groups at δ 2.91, 2.85 and 2.43 ppm respectively. Substituted triazole compound (9) was achieved by the conversion of compound (8) throughout methylation of the thiol group presented in the triazole ring using methyl iodide in the presence of methanol. The structure of the resulted compound has been confirmed by ^{1}H-NMR which showed two singlets at δ 2.65 and 2.60 ppm related to methyl groups in the triazole ring. The Schiff bases (10,11) have been achieved effectively by the reaction of substituted acetophenone with acid hydrazide (4) in ethanol. The formation of the products has been confirmed by IR spectra which showed a band at 1603 cm^{-1} belongs to azomethine group (CH=N) stretching. The ^{1}H-NMR for nitro-substituted compound (10) showed a signal at 2.55 ppm as a singlet corresponding to the methyl protons while it was showed a singlet at 2.63 ppm related to methyl group for chloro-substituted compound (11).

EXPERIMENTAL PART

General

All chemicals from BDH and Fluka companies. They were used without purification. Solvents were distilled, dried by using dry



Scheme 1: Synthesis of compounds (1-11)

sieves. Thin Layer Chromatography analysis has been achieved on an aluminum foil. melting points were measured using (Electro Thermal IA1900). Infrared spectra were determined as KBr solid pellets on (Shimadzu FT- IR-8400). ^{1}H-NMR spectra were recorded using a Varian Agilant USA 500 MHz spectrometer in central Laborite of Tehran University, using DMSO as a solvent.

Synthesis

General Procedure

3-(p-nitrophenyl)-1-phenylprop-2-en-1-one / Synthesis of Chalcone (1)

Acetophenone (0.1 mol) and (0.1 mol) of 4-nitrobenzaldehyde were dissolved in (60 mL) of EtOH, then solution of NaOH (40%) has been added, stirring the reaction mixture for (5 hours), the reaction mixture has been filtered, washed with H_2O, recrystallized with absolute EtOH to give yellow powder (yield: 71%; m.p: 159-161°C) δ_H: (500 MHz, DMSO-d_6) 8.30 (2H, doublet), 8.13 (1H, doublet),7.82 (2H, doublet), 7.77 (2H, doublet), 7.74 (1H, doublet), 7.55–7.48 (1H, multiplet), 7.45 (2H, triplet).

2-((1-(p-nitrophenyl)-3-oxo-m-phenylpropyl)thio)acetic acid (2)

2-Mercaptoacetic acid (0.01 mol) was added to (0.01 mol) of chalcone (1) followed by addition of (1-mL) of (25% NaOH) in (40 mL) ethanol, stirring the reaction for (5 hours) at r.t. then, neutralized using conc. HCl. The formed precipitate has been filtered and recrystallized from EtOH and water to produce an orange powder (yield: 81%; m.p.:182–184°C) δ_H: (500 MHz, DMSO-d_6) 9.62 (1H, single), 8.19 (2H, doublet), 7.95 (2H, doublet of doublet), 7.49 (2H, doublet), 7.47–7.42 (1H, multiplet), 7.37 (2H, triplet), 4.34 (1H, triplet), 3.85 (1H, doublet of doublet), 3.41 (2H, singlet), 3.26 (1H, doublet of doublet).

Ethyl 2-((1-(4-pitrophenyl)-3-oxo-m-phenylpropyl)thio) acetate (3)

The addition of concentrated sulfuric acid (2 mL) to compound (2) (0.01 mol) in EtOH (75 mL) was achieved slowly at zero degree with stirring. The mixture was refluxed for (6h), neutralized by 5% aqueous Na2CO3, the excess of ethanol evaporated. The aqueous layer has been re-extracted using CH2Cl2 (2×20 mL), then dried over magnesium sulphate, filtered, and concentrated to give brown solid (Yield: 73%; m.p.: 103–105°C) δH: (500 MHz, DMSO-d6) 8.18 (2H, doublet), 7.91 (2H, doublet of doublet), 7.47 (2H, doublet of doublet), 7.47–7.41 (1H, multiplet), 7.38 (2H, triplet), 4.35 (1H, triplet), 4.18 (2H, quartet), 3.75 (1H, doublet of doublet), 3.52 (2H, singlet), 3.29 (1H, doublet of doublet), 1.38 (1H, triplet).

2-((1-(p-nitrophenyl)-3-oxo-m-phenylpropyl)thio acetohydrazide (4)

To a mixture solution of compound (3) (0.1 mol) in (50 mL abs. EtOH), (10 mL) of N2H4.H2O 85% was added. The reaction has been refluxed for (4 hours). TLC has been used to follow up the of reaction, solvent then evaporated to give acid hydrazide (4) as a pale brown solid, which was recrystallized from ethanol (yield : 92%; m.p. 286-288°C) δH: (500 MHz, DMSO-d6) 8.18 (2H, doublet), 7.85 (2H, doublet of doublet), 7.48 (2H, doublet), 7.47 – 7.42 (1H, multiplet), 7.37 (2H, triplet), 6.31 (1H, singlet), 4.35 (1H, triplet), 3.61 (1H, doublet of doublet), 3.36 – 3.29 (3H, multiplet), 2.83 (1H, singlet), 1.85 (1H, singlet).

Potassium2-(2-((1-(4-nitrophenyl)-3-oxo-3-phenylpropyl) thio)acetyl)hydrazine-1-carbodithioate (5)

Carbon disulfide (6 mL) has been added to (0.01 mol) of compound (4) dissolved in KOH (0.23 g/50 mL ethanol). The mixture was then stirred for (5 hours) at r.t. The solvent has been concentrated under vacuum; the residue was decanted in water then acidified with dilute hydrochloric acid. The resulted product has been filtered, recrystallized from methanol, (yield 85%; m.p.: 320–322°C) δ_H: (500 MHz, DMSO-d_6) 8.18 (2H, doublet), 7.85 (2H, doublet of doublet), 7.50 (2H, doublet), 7.47 – 7.41 (1H, multiplet), 7.37 (2H, triplet), 6.31 (1H, singlet), 4.35 (1H, triplet), 3.61 (1H, doublet of doublet), 3.36 – 3.27 (3H, multiplet), 2.83 (1H, singlet).

3-(((5-mercapto-1,3,4-oxadiazol-2-yl)methyl)thio)-3-(p-nitrophenyl)-1-phenylpropan-1-one (6)

To a solution of acid hydrazide compound (4) (0.05 mol) and (0.56 g of KOH in EtOH 80 mL), (6 mL, 0.1 mole) of CS_2 has been added dropwise. The mixture has been refluxed for (24 hours). TLC has been used to monitor the end of reaction, solvent evaporated, cooled, poured on ice-water (50 mL), acidified with dilute HCl (pH=5-6), the solid product was obtained by filtration and purified by recrystallization from ethanol (yield: 51%; m.p.: 295–297 °C) δ_H: (500 MHz, DMSO-d_6) 8.15 (2H, doublet), 7.83 (2H, doublet of doublet), 7.47 – 7.39 (3H, multiplet), 7.35 (2H, triplet), 4.35 (1H, triplet), 3.71 (2H, singlet), 3.55 (1H, doublet of doublet), 3.31 (1H, doublet of doublet), 2.00 (1H, singlet).

3-(((5-(benzylthio)-1,3,4-oxadiazol-2-yl)methyl)thio)-3-(p-nitrophenyl)-1-phenylpropan-1-one (7)

A solution mixture of compound (6) (0.01 mol) has been dissolved in (30 mL) of methanol and aqueous solution of NaOH 20% (1-mL), then benzyl bromide (0.01 mol) was added. After reflux for (24 hours), the product filtered and dried, recrystallized from EtOH to offer a pale brown solid (yield : 55%; m.p. 221–223°C) δH: (500 MHz, DMSO-d6) 8.15 (2H, doublet), 7.82 (2H, doublet of doublet), 7.48–7.41 (3H, multiplet), 7.37 (2H, triplet), 7.23–7.10 (5H, multiplet), 4.35 (1H, triplet), 4.30 (2H, singlet), 3.79 (2H, singlet), 3.51 (1H, doublet of doublet), 3.07 (1H, doublet of doublet).

3-(((4-amino-5-mercapto-4H-1,2,4-triazol-3-yl) methyl)thio)-3-(p-nitrophenyl)-1-phenylpropan-1-one (8)

Compound (5) (0.1 mol) was dissolved in absolute ethanol (15 mL) then (0.28 mL) of hydrazine hydrate was added. The reflux was carried out for (6 hours), after that the mixture cooled, acidified with (2N) HCl and filtered off, dried, recrystallized from methanol /water (yield: 61%; m.p.: 166-168°C) δH: (500

Table 1: Physical data of compounds (1-11).

Comp. no.	*Molecular formula*	*Yield (%)*	*Melting point (°C)*	*Color*
1	$C_{15}H_{11}NO_3$	71	159-161	Yellow
2	$C_{17}H1_5NO_5S$	81	182-184	Orange
3	$C_{19}H_{19}NO_5S$	73	103-105	Brown
4	$C_{17}H_{17}N_3O_4S$	92	286-288	Dark yellow
5	$C_{18}H_{16}KN_3O_4S_3$	85	320-322	White
6	$C_{18}H_{15}N_3O_4S_2$	51	295-297	Pale orange
7	$C_{25}H_{21}N_3O_4S_2$	55	221-223	Pale brown
8	$C_{18}H_{17}N_5O_3S_2$	61	166-168	White
9	$C_{20}H_{21}N_5O_3S_2$	65	141-143	Dark brown
10	$C_{25}H_{22}N_4O_6S$	63	171-173	White
11	$C_{25}H_{22}ClN_3O_4S$	52	201-203	White

Table 2: Spectral data of synthesized compounds (1-11).

Comp. no.	*IR (KBr) v cm^{-1}*										
	O-H	*C-O-C*	*NO2 sy*	*NO2 asy*	*C=S*	*C=N*	*C=O*	*N-H2*	*NH*	*C=C*	*S-H*
1	-	-	1253	1357	-	-	1670	-	-	1601	-
2	3402	-	1313	1415	1198	-	1709 1663	-	-	-	-
3	-	-	1246	1416		-	1746 1667	-	-	-	-
4	-	-	1309	1375	-	1665	1688 1665	3516 3495	3442	-	-
5	-	-	1346	1423	1188	-	1661	-	3214 3327	-	-
6	-	1070	1338	1419	1173	1645	1670	-	-	-	2373
7	-	1089	1361	1397	-	1653	1760	-	-	-	
8	-	-	1338	1446	1198	1581	1701	3473 3356	-	-	2366
9	-	-	1417	1427	-	1570	1705	-	3455		-
10	-	-	1342	1442	-	1600	1669 1607		3183	-	-
11	-	-	1420	1428	-	1603	1692 1660	-	3110	-	-

MHz, DMSO-d6) 8.15 (2H, doublet), 7.84 (2H, doublet of doublet), 7.46 (2H, doublet), 7.44–7.39 (1H, multiplet), 7.36 (2H, triplet), 4.35 (1H, triplet), 4.04 (2H, singlet), 3.59 (1H, doublet of doublet), 3.34 (1H, doublet of doublet), 2.91 (1H, singlet), 2.85 (1H, singlet), 2.43 (1H, singlet)

3-(((4-(methylamino)-5-(methylthio)-4H-1,2,4-triazol-3-yl) methyl)thio)-3-(p-nitrophenyl)-1-phenyl -propan-1-one (9)

A solution of sodium acetate (0.002 mol) and (0.02 mol) methyl iodide in (50 mL) ethanol was added to compound (8) (0.01 mol). The mixture has been refluxed for (4 hours). TLC was used to monitor the reaction, after that the mixture of the reaction poured onto crushed ice, extracted with CH2Cl2 then, filtered, concentrated to produce dark brown solid (yield : 65%; m.p. 141-143°C) δH: (500 MHz, DMSO-d6) 8.17 (2H, doublet), 7.84 (2H, doublet of doublet), 7.46 (2H, doublet), 7.44–7.39 (1H, multiplet), 7.37 (2H, triplet), 4.35 (1H, triplet), 4.04 (2H, singlet), 3.58 (1H, doublet of doublet), 3.33 (1H, doublet of doublet), 2.98 (1H, singlet), 2.65 (3H, singlet), 2.60 (3H, singlet).

N'-(1-(4-chlorophenyl)ethylidene)-2-((1-(p-nitrophenyl)-3-oxo-m-phenylpropyl)thio) acetohydrazide(10)

A mixture of (0.01 mol) of compound (4), (50 mL) of ethanol and (0.01 mol) of 4-nitro acetophenone, were refluxed for (4 h) then cooled to r.t. The resulted solid has been collected through filtration, then dried. The product was redissolved in ethanol for crystallizations and then dried to give a product (yield: 63%; m.p. 171-173°C δ_H: (500 MHz, DMSO-d_6) 8.18 (2H, doublet), 7.88 (2H, doublet of doublet), 7.51 (4H, quarted), 7.46 (2H, doublet), 7.44–7.42 (1H, multiplet), 7.36 (2H, triplet), 4.35 (1H, triplet), 3.46–3.38 (3H, multiplet), 3.13 (1H, doublet of doublet), 2.55 (3H, singlet).

2-((1-(4-nitrophenyl)-3-oxo-3-phenylpropyl)thio)-N'-(1-(4-nitrophenyl) ethylidene)acetohydrazide (11)

Compound (4) (0.01 mol) has been dissolved in (50 mL) ethanol, then (0.01 mol) of 4-chloro acetophenone has been added. The mixture was refluxed for (2.5 hours) then cooled to r.t. The resulted solid has been collected through filtration and dried. The product was redissolved in hot ethanol for recrystallization and then dried to give the title compound (yield: 52%; m.p. 201–203°C) δH: (500 MHz, DMSO-d6) 8.36 (2H, doublet), 8.19 (2H, doublet of doublet), 7.86 (2H, doublet of doublet), 7.54 (4H, doublet of doublet), 7.47–7.40 (1H, multiplet), 7.37 (2H, triplet), 4.34 (1H, triplet), 3.61 (1H, doublet of doublet), 3.53 (2H, singlet), 3.41 (1H, doublet of doublet), 2.63 (3H, singlet).

CONCLUSION

We have successfully synthesized a new substituted of 1,2,4-triazole; 1,3,4- oxadiazol and Schiff base moieties including chlorophenyl and nitrophenyl ring using chalcone compound as starting material. Additional efforts are proceeding to use these compounds as versatile building blocks to synthesize interesting molecules that can be applied in medicinal chemistry.

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