Synthesis of Some Schiff's Bases Containing 1,3,4-Thiadiazole Ring and Their Properties as Antioxidants

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Abstract

A series of Schiff's bases containing 1,3,4-thiadiazole (2,5-di(N-substitutedbenzylideneamino)-1,3,4-thiadiazole) were prepared through the reaction of thiosemicarbazide with chloro cyanide. The product was directly reacted with benzaldehyde and substituted benzaldehydes. The synthetic compounds (0-10) were identified using the analytical and spectral means. The antioxidant properties were measured of the prepared compounds using the metal ions (Fe^{+3}, Cu^{+2}), and Ferrozine and 2,9-dimethyl-1,10-phenanthroline (neocuproine). The results showed that the compound no. 5 [2,5-di(N-(4-hydroxybenzylideneamino)-1,3,4-thiadiazole] reveals the highest antioxidant activity through this work.

Introduction

The progress achieved in the synthesis of heterocyclic compounds with a biological potential is due to improvement of the methodological study of tested substances too.

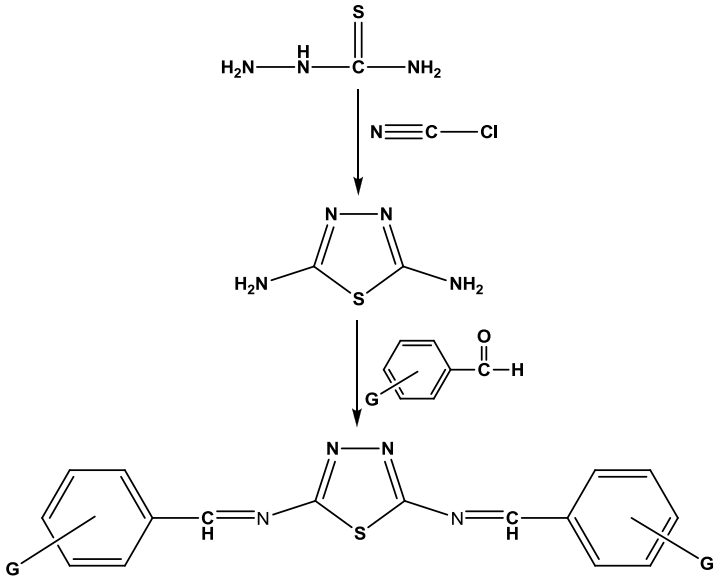
It is known that many 1,3,4- thiadiazole and 1,2,4-triazole derivatives have biological activity, with their antibacterial [1-3], antimycobacterial [4,5], antimycotic [6], antifungal [7,8], antidepressive [9], and cardiotonic [10] action being notable.

Recent research has also established for these heterocycles an analgesic [11] and anti-inflammatory [12,13] activity. Meanwhile, N-acylated amino acids are known for their hepatoprotective [14], antimicrobial [15,16] and antitumoral [17,18] action.

In the view of the facts mentioned above and as part of our initial efforts to discover potentially active new agents. Hence, it has been reported that 1,3,4-thiadiazole derivatives were widely used for their antioxidant activity [19].

Experimentals and Methods

The synthesis of the target molecule is shown in the sequences of reactions depicted in the following scheme. The FTIR spectral data were recorded on FTIR-8300 Fourier Transform Infrared Spectrophotometer SHIMADZU using potassium bromide disc. Double-beam UV-Visible spectrophotometer (UV 1650 CP), SHIMADZU. Melting points (^oC) were recorded on hot stage Gallen Kamp melting point apparatus and were uncorrected. Chemical names follow IUPAC nomenclature.



2,5-di(N-substitutedbenzylideneamino)-1,3,4-thiadiazole

Scheme.

1) Synthesis of 2,5-diamino-1,3,4-thiadiazole:

Thiosemicarbazide (0.02 mole) was dissolved in (50 ml) of absolute ethanol, chlorocyanide (0.02 mole) was added to this solution and the reaction mixture was refluxed for (6 hrs.)[20]**,** the resultant solution was poured onto crushed ice, the solid obtained was filtered and recrystallized from ethanol, the yield was (60%), the melting point was (185 ^{o}C), the compound was directly used in the next step. The FTIR (KBr cm^{-1}) spectral data for this compound are as follows 3210-3100 (asym. and sym. stretching vibration of NH_2 group), 1620 (cyclic C=N).

2) Synthesis of 2,5-di(N-substitutedbenzylideneamino)-1,3,4-thiadiazole:

2,5-diamino-1,3,4-thiadiazole (0.01 mole) was dissolved in absolute ethanol (50 ml), benzaldehyde or substituted benzaldehyde (0.01 mole) was slowly added to the refluxed mixture, the net mixture was refluxed for (7 hrs.) with stirring, the reflux was completed for another two hours until no more precipitate formed. After cooling to room temperature the mixture was filtered and the precipitate was dried and recrystallized from ethanol, the yield was (60%), the melting point of the target molecule was (190 ^{o}C). The same reaction was carried out to different substituted benzaldehyde (G: H, *p*-Cl, *p*-Br, *p*-OCH_3, *p*-NO_2, *p*-OH, *m*-Cl, *m*-Br, *m*-OCH_3, *m*-NO_2, *m*-OH). The FTIR (KBr cm^{-1}) spectral data (stretching vibrations) for the compounds (0-10) are shown below in Table (1). The physical properties of the compounds (0-10) are shown in Table (2).

Table (1)
The FTIR (KBr cm^{-1}) spectral data (stretching vibrations) for the compounds (0-10).

G	*Compd.*	*O-H*	*C-H aromatic*	*C-H aliphatic*	*C=N*	*C=C aromatic*
H	0	-	3070	-	1617	1608
p-Cl	1	-	3063	-	1620	1567
p-Br	2	-	3100	-	1627	1588
p-OCH_3	3	-	3105	2933-2794	1634	1590
p-NO_2	4	-	3100	-	1620	1590
p-OH	5	3382	3082	-	1625	1600
m-Cl	6	-	3030	-	1616	1571
m-Br	7	-	3007	-	1620	1587
m-OCH_3	8	-	3020	2950-2805	1623	1600
m-NO_2	9	-	3034	-	1629	1603
m-OH	10	3360	3042	-	1612	1602

Table (2)
The melting point and yield of the compounds (0-10).

G	*Compd.*	*M.P. (^oC)*	*% Yield*	*IUPAC Name*
H	0	190-192	80	2,5-di(N-benzylideneamino)-1,3,4-thiadiazole
p-Cl	1	192-194	75	2,5-di(N-(4-chlorobenzylideneamino)-1,3,4-thiadiazole
p-Br	2	203-205	70	2,5-di(N-(4-bromobenzylideneamino)-1,3,4-thiadiazole
p-OCH_3	3	188-190	84	2,5-di(N-4-methoxybenzylideneamino)-1,3,4-thiadiazole
p-NO_2	4	197-199	66	2,5-di(N-(4-nitrobenzylideneamino)-1,3,4-thiadiazole
p-OH	5	210-212	82	2,5-di(N-(4-hydroxybenzylideneamino)-1,3,4-thiadiazole
m-Cl	6	177-179	65	2,5-di(N-(3-chlorobenzylideneamino)-1,3,4-thiadiazole
m-Br	7	191-193	71	2,5-di(N-(3-bromobenzylideneamino)-1,3,4-thiadiazole
m-OCH_3	8	185-187	77	2,5-di(N-(3-methoxybenzylideneamino)-1,3,4-thiadiazole
m-NO_2	9	198-200	81	2,5-di(N-(3-nitrobenzylideneamino)-1,3,4-thiadiazole
m-OH	10	203-205	88	2,5-di(N-(3-hydroxybenzylideneamino)-1,3,4-thiadiazole

3) Ferric ion (Fe^{+3}) antioxidant properties:

The antioxidant properties of the prepared compounds containing 1,3-oxazoline ring reduce (Fe^{+3} to Fe^{+2}) were measured by using ferrozine [21]. The reduction of (Fe^{+3}) by 1,3-oxzoline was studied at pH 5.5, due to low solubility of iron at physiological pH, the reaction mixture contained 50 mM sodium acetate buffer (pH 5.5). 1 mM ferrozine, 50, 100 μM of tested compounds and 100 μM of $Fe(NO_3)_3$. The reaction was started by the addition of $Fe(NO_3)_3$ and the increase of absorbance at 562 nm after 3 minutes was recorded, Fe^{+2} concentration was determined by using an extinction coefficient for $Fe(ferrozine)_3^{+2}$ complex which is equal to 27.9×10^3 M^{-1} $.cm^{-1}$ [22].

4) Copper ion (Cu^{+2}) antioxidant properties:

The antioxidant properties of the prepared compounds containing 1,3-oxazoline ring reduce (Cu^{+2} to Cu^{+1}) were measured by using 2,9-dimethyl-1,10-phenanthroline (neocuproine) [23], an indicator molecule that binds specifically to the reduced form of copper (Cu^{+1} but not to the oxidized form Cu^{+2}) [24]. The reaction mixture contained (20 mM) KH_2PO_4/KOH buffer (pH 7.4), 200 μM $Cu(NO_3)_2$, 600 μM 2,9-dimethyl-1,10-phenanthroline, 50, 100 μM of the tested compounds.

The mixtures were incubated at room temperature for 120 minutes and then the absorbances were recorded at 455 nm. The copper concentration was determined by using an extinction coefficient for $Cu(neocuproine)_2^{+2}$ complex which is 7.2×10^3 mM^{-1} $.cm^{-1}$, that was determined by reducing Cu^{+2} with ascorbate [23].

Results and Discussion

The synthesis of 2,5-di(N-substitutedbenzylideneamino)-1,3,4-thiadiazole was achieved by the reaction of thiosemecarbazide with chloro cyanide in absolute ethanol, the product was reacted with benzaldehyde and substituted benzaldehyde to form the target molecules (0-10). The authenticity of the product was confirmed by spectral data (FTIR) shown in Table (1). The antioxidant properties of the prepared

compounds are assessed by the extent of conversion of the Fe^{+3} and Cu^{+2} to the reduced form Fe^{+2} and Cu^{+1}).

The antioxidant properties of the compounds were studied at different concentrations. The antioxidant activity of putative antioxidant has been attributed to various mechanisms, among which are prevention chain initiation, binding of transition metal ion catalyst, decomposition of peroxides, prevention of continued hydrogen abstraction, reductive capacity and radical scavenging [25]. The compound (5) reveals the highest antioxidant activity this is attributed to the presence of hydroxyl group in the *p*-position of the benzene ring. Thiadiazoles (0-10) studied show higher reducing capacity for copper ions than for iron ions, this can be attributed to the standard reduction and oxidation potentials of the metals, the standard reduction potential of the Cu^{+2}/Cu^{+1} (0.15 V) which is much lower than that for Fe^{+3}/Fe^{+2} (0.77 V). Table (3) and Table (4) show the antioxidant properties of compounds (0-10).

Note the standard deviation (SD) referred to (±) of at least three independent experiments was calculated and showed in the results.

Table (3)
The antioxidant values of compounds (0-10) against Fe^{+2}.

µmole Fe^{+2}/µmole 1,3,4-thiadiaozle			
Compd.	***G***	***50 µM***	***100 µM***
0	H	0.0075±0.001	0.0058±0.001
1	*p*-Cl	0.0052±0.001	0.0010±0.001
2	*p*-Br	0.0042±0.000	0.0028±0.001
3	*p*-OCH_3	-	0.0023±0.000
4	*p*-NO_2	0.0031±0.001	0.0019±0.002
5	*p*-OH	0.0330±0.002	0.0500±0.001
6	*m*-Cl	0.0023±0.001	0.0018±0.001
7	*m*-Br	0.0029±0.001	0.0010±0.001
8	*m*-OCH_3	0.0040±0.002	0.0012±0.001
9	*m*-NO_2	0.0045±0.003	0.0032±0.000
10	*m*-OH	0.0090±0.000	0.0294±0.001

Table (4)
The antioxidant values of compounds (0-10) against Cu^{+1}.

µmole Cu^{+1}/µmole 1,3,4-thiadiazole			
Compd.	***G***	***50 µM***	***100 µM***
0	H	0.20±0.001	0.33±0.000
1	*p*-Cl	0.23±0.001	0.36±0.001
2	*p*-Br	0.38±0.000	0.51±0.001
3	*p*-OCH_3	0.49±0.002	0.62±0.002
4	*p*-NO_2	0.25±0.003	0.43±0.002
5	*p*-OH	0.68±0.001	0.90±0.001
6	*m*-Cl	0.08±0.001	0.18±0.001
7	*m*-Br	0.18±0.004	0.31±0.001
8	*m*-OCH_3	0.31±0.001	0.44±0.000
9	*m*-NO_2	0.21±0.004	0.32±0.002
10	*m*-OH	0.39±0.001	0.56±0.001

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الخلاصة

تم في هذا البحث تحضير مركبات (قواعد شف) مرتبطة بحلقة ٤,٣,١- ثاياديازول المسماة [2,5-di(N-substitutedbenzylideneamino)-1,3,4-thiadiazole]، وذلك من خلال مفاعلة ثايوسيميكاربازايد مع كلورو سايانيد والناتج تمت مفاعلته بعد ذلك مع البنزالديهايد غير المعوض وعدة مركبات من البنزالديهايد المعوض وتم تشخيص المركبات بالوسائل التحليلية والطيفية، وتم قياس فعالية هذه المركبات (٠-١٠) كمضادات للأكسدة بأستخدام أيونات المعدنين (Fe^{+3}، Cu^{+2}) وذلك بأستخدام كاشف الفيروزين و كاشف ٩,٢-ثنائي مثيل-١٠,١-فينانثرولين.(نيوكبروين)، أظهر المركب رقم (٥) [2,5-di(N-(4-hydroxybenzylideneamino)-1,3,4-thiadiazole] أعلى فعالية كمضاد للأكسدة من خلال هذا البحث.