Synthesis And Antibacterial Activity Of Some New α-Phenylcinnamoyl Thiosemicarbazides And 5-Substituted- α-Phenylstyryl-1,3,4-Triazole-2-Thiols

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Abstract

A series of new derivatives of α-phenylcinnamoyl thiosemicarbazides have been synthesized and converted to 5-substituted- α-phenylstyryl-1,3,4-triazole-2-thiols.These compounds were screened for their antibacterial activity against Staphylococcus aureus ,Escherichia coli and pseudomonas aeruginosa. It was found that α- phenylcinnamoyl thiosemicarbazides were more active than triazoles against Staphylococcus aureus and Escherichia coli.

Introduction

In continuation with our earlier work(1,2,3) on the synthesis and screening of substituted thiosemicarbazides, triazoles,oxadiazoles and thiadiazoles , and in view of the fact that hardly any work has been reported on the synthesis of derivatives of styryl and α-phenylstyryl substituted thiosemicarbazides and heterocyclic substituted derivatives ,it was thought of interest to synthesize new α-phenylstyryl substituted thiosemicarbazides and triazoles with the hope that the resulting products may prove to be better anti-bacterials.

Experimental

Materials:Benzaldehyde derivatives and phenylacetic acid were of Aldrich and Fluka products and were used without purification. α-phenylcinnamic acid derivatives were prepared in our laboratory by known methods(4).The physical properties of the synthesized α-phenylcinnamic acid derivatives are given in Table 1.

Apparatus: Melting points were determined on a Gallencamp hot stage and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 375B spectrophotometer as KBr discs. ^{1}Hnmr spectra were determined on a Varian HA 80 MHz pulse nmr spectrometer using DMSO-d_6 as solvent and TMS as internal reference. Microanalyses were performed by the analytical laboratories of Petroleum Exploration Company,Baghdad.

Preparation of Substituted α-Phenylcinnamoyl Thiosemicarbazides

Substituted α-phenylcinnamoyl thiosemicarbazides were synthesized by the method of Hoggarth(5) as described earlier(3)for the synthesis of cinnamoly thiosemicarbazide from cinnamoly chloride and thiosemicarbazide. The physical and analytical properties of the synthesized α-Phenylcinnamoyl Thiosemicarbazides are given in the Table2.

Preparation of 5-(Substituted- α -Phenylstyryl)-1,3,4-Triazole-2-Thiols

Substituted α-phenylcinnamoyl thiosemicarbazides (0.02 mole) in sodium ethoxide or methoxide (40 ml;2N) was stirred and heated on a water path for 6 hrs. The hot solution was filtered, cooled to room temperature and acedified with dilute hydrochloric acid (10%). The precipitate was filtered and recrystallized from an appropriate solvent. The physical and analytical properties of the synthesized (substituted- α-phenylstyryl)-1,3,4-triazole-2-thiols are given in Table 3 .

Biological methods

The antibacterial activity of the synthesized compounds were determined by the agar diffusion method of Kirby and Baur(6). Each compound was tested twice and their average values are reported in Tables 2 and 3.

Results And Discussion

Substituted α-phenylcinnamoyl thiosemicarbazides were prepared by the acid chloride method of Hoggarth (5). Intramolecular dehydration by the action of sodium ethoxide afforded the corresponding 5-substituted- α-phenylstyryl-1,3,4-triazole-2-thiols.

The structure and the physical properties of the synthesized compounds are given in Tables 1, 2 and 3. The ir spectra of Substituted α-phenylcinnamoyl thiosemicarbazides are characterized by the presence of three principle bands. A band appearing at 1540-1590 cm^{-1} is assigned to NH bending vibration. The band at 1310-1380 cm^{-1} is due to C-N stretching vibration, while the band appearing in the range 995-1030 cm^{-1} is assigned to the thione C=S stretching vibration (7).

The ir spectra of 5-substituted- α-phenylstyryl-1,3,4-triazole-2-thiols showed the presence of a C=N stretching absorption at 1610-1660 cm^{-1} , a broad band at 3330-3500 cm^{-1} due to NH stretching, and a band at 1639-1689 cm^{-1} assigned to the olefinic C=C bond. In certain instances as in compounds 26 &27 , the C=C and C=N stretching absorption coalesce together to give single bands at 1666 and 1669 cm^{-1} respectively. While the aromatic C=C double bond showed two stretching bands at 1562-1607 cm^{-1} and 1460-1515 cm^{-1} regions.

The $^{[1]}$H-nmr spectra of α-phenylcinnamoyl thiosemicarbazides showed three characteristic bands. A downfield singlet at 9.0-10 ppm due to the –CONH- group, a second singlet in the range 8.7-9.2 ppm assigned to –CS-NH-

group and the $–NH_2$ group showed a singlet in the region 2.8 -3.3 ppm . The olefinic proton in these compounds showed a singlet in the range 7.60 ppm to 7.78 ppm, which is in a lower region than the same proton in the corresponding α-unsubstituted cinnamic acid derivatives. This is partly due to ring currents of the two aromatic rings which are trans to each other and flank the olefinic proton H_8 and partly due to the anisotropy affect of the carbonyl group as this proton lies in the deshielding zone of the C=O group as shown in Figur 1 .

The ^{1}H-nmr spectra of substituted-α-phenylstyryl-1,3,4-triazole-2-thiols showed an NH signal at 13.03-13.50 ppm together with an SH signal at 2.2-2.5 ppm with variable intensity. The integration of these two signals is equivalent to one proton. This is in accordance with the fact that these compounds exist as a tautomeric mixture of the thione and thiol forms with the predomenance of the thione form (8).

Biological Activity

The antibacterial activity of the title compounds towards three types of bacteria was determined by the agar diffusion method (6). The test organisms were Staphylococcus aureus, Escherichia Coli and Pseudomonas aeruginosa. The results indicate that α- phenyl Substituted cinnamoyl thiosemicarbazides, α-phenylstyryl-1,3,4-triazole-2-thiols possess the highest activity among the aromatic acid derivatives (1-3). It is probable that the presence of the double bond together with the two aromatic rings with the active groups like thiosemicarbazides or triazole ring are the active sites in these classes of compounds which enable them to bind to cell walls in these organisms. At present the possibility of the liberation of the parent acid hydrazides and thiosemicarbazides, the intermediates in the synthesis of triazoles, by metabolic degredation to be responsible for antibacterial activity can not be ruled out (9). Another possibility for the mechanism of action of these compounds is through complexation with the metals present at the active sites of some important enzymes such as the zinc ion in alkaline phosphatase or iron present in ribonucleotide diphosphate reductase (RDR) (10).

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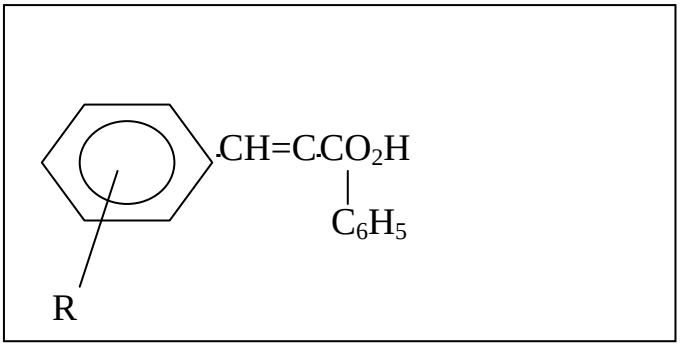
Table [1] Physical Properties of α-phenylcinnamic acid Derivatives.



Compound No.	R	Molecular Formula	M.P.(c^o)	Yield %
1	H	$C_{15}H_{12}O_2$	162-164	80
2	2,6-Di-C1	$C_{15}H_{10}O_2Cl_2$	239-241	96
3	o-NO_2	$C_{15}H_{11}NO_4$	201-203	70
4	m-NO_2	$C_{15}N_{11}NO_4$	163-165	82
5	p-NO_2	$C_{15}N_{11}NO_4$	208-209	95
6	p-CH_3	$C_{16}H_{14}O_2$	168-170	78
7	m-OCH_3	$C_{16}H_{14}O_3$	186-188	84
8	p-OCH_3	$C_{16}H_{14}O_3$	191-193	65
9	o,m-Di-OCH_3	$C_{17}H_{16}O_4$	145-147	77
10	o,p-Di-OCH_3	$C_{17}H_{16}O_4$	187-189	60
11	o-OH	$C_{15}H_{12}O_3$	195-197	90
12	p-OH,m-OCH_3	$C_{16}H_{14}O_4$	191-193	85
13	m,p-Di-OH	$C_{15}H_{12}O_4$	188-190	75

Table [2] Physical and Antibacterial Properties of α-Phenylcinnamoyl Thiosemicarbazides .R-C_6H_4 –CH=C(C_6H_5)-$CONHNHCSNH_2$

Compound No.	R	Molecular Formula	M.P.(c^o)	Yield %	Antibacterial Activity		
					S. aureus	E. coli	Ps.aer
14	H	$C_{16}H_{15}N_3OS$	222-224	70	++	+	+ -
15	2,6-Di-C1	$C_{16}H_{13}Cl_2N_3OS$	206-208	97	+++	++	+
16	o-NO_2	$C_{16}H_{14}N_4O_3S$	213-215	90	++	++	+
17	m-NO_2	$C_{16}H_{14}N_4O_3S$	200-202	89	++	++	+
18	p-NO_2	$C_{16}H_{14}N_4O_3S$	204-206	75	+++	++	+
19	p-CH_3	$C_{17}H_{17}N_3OS$	219-220	93	++	+	+-
20	m-OCH_3	$C_{17}H_{17}N_3O_2S$	176-178	71	+	+	-
21	p-OCH_3	$C_{17}H_{17}N_3O_2S$	214-216	88	++	++	+
22	o,m-Di-OCH_3	$C_{18}H_{19}N_3O_3S$	227-229	85	+-	-	+

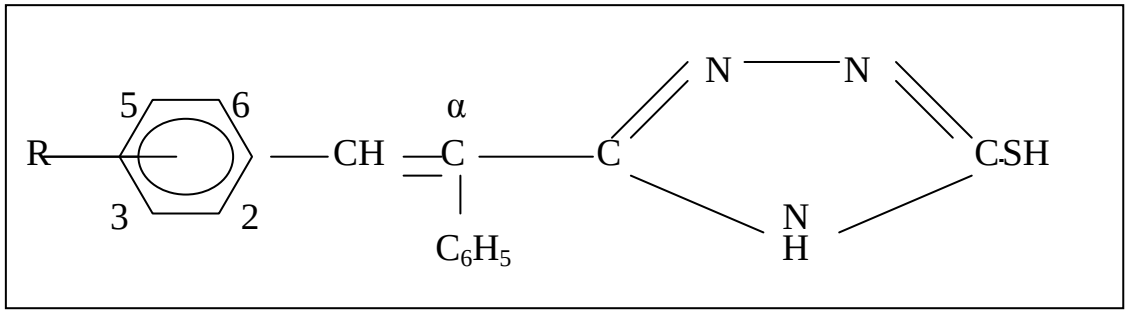
Abbreviations

- = no Inhibition, +- =weak, + =medium, ++ =high, +++ =more high

Notes:

There was good a greement between C.H.N found and calc.

Table [3] Physical and Antibacterial Properties of 5-Substituted- -Phenylstyryl-1,3,4-Triazole-2-Thiols.



Compound No.	R	Molecular Formula	M.P.(c^o)	Yield %	Antibacterial Activity		
					S. aureus	E. coil	Ps.aer
23	H	$C_{16}H_{13}N_3OS$	176-178	75	++	+	-
24	2,6-Di-C1	$C_{16}H_{11}Cl_2N_3OS$	240-242	77	++	+	+
25	p-CH_3	$C_{17}H_{15}N_3S$	248-250	69	+	+-	+
26	m-OCH_3	$C_{17}H_{15}N_3OS$	186-188	65	++	+	+-
27	p-OCH_3	$C_{17}H_{15}N_3OS$	180-182	75	+	-	+

Table 4 Ir and ^{1}H-nmr Spectral Data for Selected α-phenylcinnamic acids, α-Phenylcinnamoyl thiosemicarbazides and 5-Substituted- α-Phenyl Styryl -1,3,4-Triazole-2-Thiols.

Compound No.	IR, νmax(cm^{-1}) OH or NH, C=0, C=C, Ar.	NMR Parameters, δ(ppm)
1	2985m, 1672s, 1640m, 1612m, 1492s.	7.13(m,5H,ArH),7.31(m,5H,α Ph),7.72(s,1H,CH=),13.5(s,1H,CO_2 H).
2	2940m, 16942, 1666sh, 1612s, 1492s.	7.31(m,3H,ArH),7.08(m,5H,α Ph),7.54(s,1H,CH=),12.97(s,1H,C O_2H).
4	3330m, 1709s, 1680s, 1575m, 1515s.	8.43(s,1H,H-2),7.9(m,4H,Ar-H,CH=),7.31(m,5H,α-Ph),13.03(s,1H,CO_2H).
14	3367m, 1672s, 1670s, 1612m, 1392s.	9.78(s,1H,CONH),9.19(s,1H,CSNH), 7.4(s,1H,CH=),7.13 (m,4H,Ar-4H),7.31(m,5H,α-Ph),3.3(s,2H,NH_2).
15	3333s, 3225s, 1680s, 1639s, 1612m, 1492s.	9.96(s,1H,CONH),9.37(s,1H,CSNH), 7.6(s,1H,CH=),7.31 (s,3H,Ar-H),7.08(s,5H,α-Ph),3.24(s,2H,NH_2).
17	3333m, 1675s, 1646s, 1612s, 1520s, 1020m.	9.96(s,1H,CONH),9.25(s,1H,CSNH), 7.7(s,1H,CH=),8.01(t,1H,H-4),7.54(m,3H,Ar-H),7.3(m,5H,α-Ph),3.24(s,2H,NH_2).
21	3389s, 3333s, 1644s, 1626s, 1612s, 1562s.	9.19(s,1H,CONH),8.78(s,1H,CSNH), 7.07(s,1H,CH=),7.02(m,5H,α-Ph),6.54(d,2H,H_2H_6),6.3 (d,2$H_{3,5}$).
24	3424m, 1689s, 1633s, 1612s, 1515s.	13.03(s,1H,NH),7.42(s,1H,CH=),7.13(m,8H,$H_{2,4}$, α-Ph).
27	3448m, 1669s, 1612s, 1515s.	13.45(s,1H,NH),7.65 (s,1H,CH=),7.2(m,5H,α-Ph),6.93(d,2H,$H_{2,6}$),6.65 (d,2H,$H_{3,5}$),3.7(s,3H,OCH_3)

Abreviations:IR, s=strong, m=medium; NMR, s=singlet, d=doublet, m=multiplet, **sh=shoulder.**

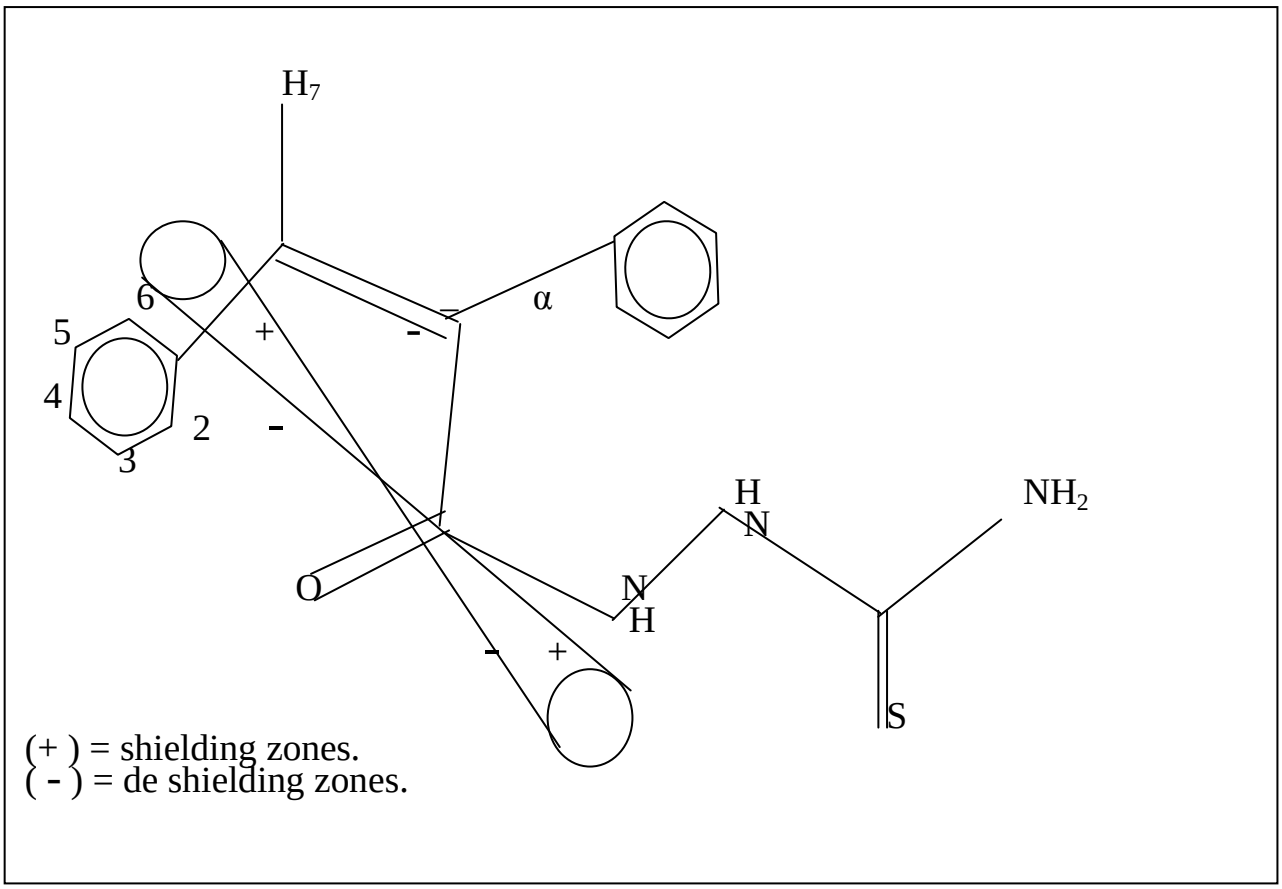


Figure 1